less of whether or not there has been a recognized trauma

Here again it is only necessary to recognize the condition and enforce rest and immobilization until union has occurred

Phalanges and Sesamoids—The phalanges of the foot are also fractured by the simplest sort of trauma, dropping something on the toe is the most frequent, stubbing the toe is probably next Many of these fractures are not easily diagnosed and, like all the other groups of the foot, demand accurate roentgen information

Many times a patient has gone round for weeks with a swollen toe, on which it has been impossible to wear a shoe, and to the chagrin of the surgeon a fracture of the phalanx or sesamoid finally is found

While the sesamoid fracture is rather rare, it should always be thought of, as it causes a long period of painful walking

Once we realize how easily a phalanx can be fractured, we shall be more likely to make roentgen diagnosis routine

COMMENT

In our recent series of forty-six cases of fractures of the foot excluding the os calcis, there were twenty-eight single and eighteen multiple fractures, and the incidence for the metatarsals was about equal except for the fourth, which was the smallest There was one fracture of the astragalus, one of the cuneiform and two of the sesamoids

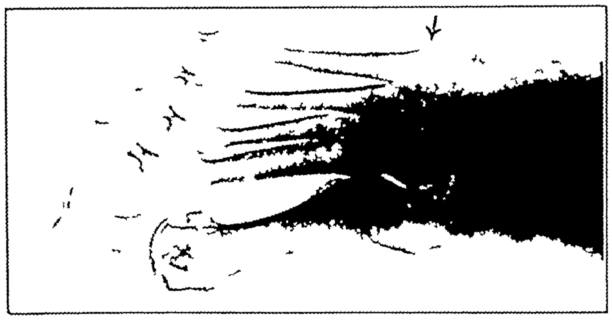

Fig 5—Sprain traction fracture of the head of the fifth metatarsal.

When we consider forty-six days the average loss of time, as reported by the Industrial Accident Commission of Ohio, for a fracture of the metatarsal, and thirty-three days for the fracture of a phalanx, as reported by Davis,[5] and also recognize that these fractures are the most common of all we can then realize the tremendous loss to labor and industry when disability is prolonged beyond the normal period because of the lack of proper diagnosis

It has often been said that if we would take as much pains in the diagnosis and treatment of fractures of the foot as we do in fractures of the hand, the results would be greatly improved

ABSTRACT OF DISCUSSION

Dr P H Kreuscher Chicago These fractures are often due to indirect violence, and the pain experienced by the patient is much less than one would ordinarily expect. Furthermore, there is often little displacement as an impaction without motion of the fractured ends frequently causes little discomfort Fractures of the smaller bones of the foot are often overlooked because the function of the foot does not depend on any one of the bones under consideration with the possible exception of the astragalus When one thinks of the bones of the foot as an arch held together by the plantar fascia, one can readily see that the stress on the injured bone is entirely different from that placed on any other bone in the body The segmented sesamoids are often congenital and are discovered only in the roentgenogram made following injury , In fractures of the astragalus it sometimes becomes necessary to do an astragalectomy If following a simple fracture of the astragalus impingement occurs on the external or internal malleolus, this can readily be dissected away In the treatment of fractures of the bones of the foot I should like to emphasize two points (1) immobilization and (2) maintenance of the long and transverse arches of the foot.

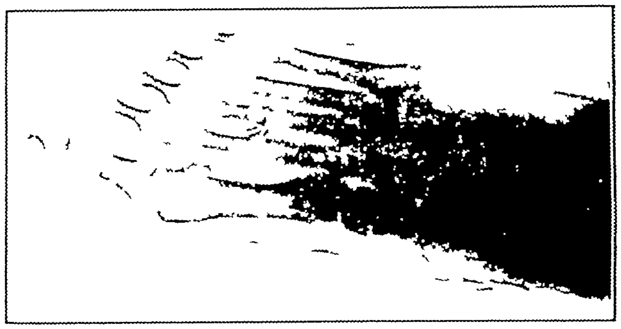

Fig 6—Fracture of the third metatarsal This case shows the importance of roentgenograms in two planes In this film the fracture was not recognized

Dr. John Dunlop Pasadena, Calif I should like to emphasize the fact that every injury of the foot that is at all questionable should be examined roentgenographically In doing industrial work I know that the one expense that the insurance companies do not mind is the money that is spent for roentgenograms and not only original but subsequent roentgenograms are advisable and permissible As to the reduction of fractures of the foot, I think that it is almost an impossible problem if there is much to be done The molding of such a foot is the thing that we have to look to If we preserve the weight-bearing in as nearly its normal line as possible we have done about all that we can do in many of these comminuted cases So far as fixation is concerned I find that in a great many minor fractures of the foot, fixation is difficult If we can improve the circulation of the part, put the patient on crutches, get active movement of the knees and keep him at rest and with the limb in an elevated position the remainder of the time, we are going to get a quicker result than by putting the extremity in plaster and cutting down the circulation thus bringing on the stiffness which we have to overcome

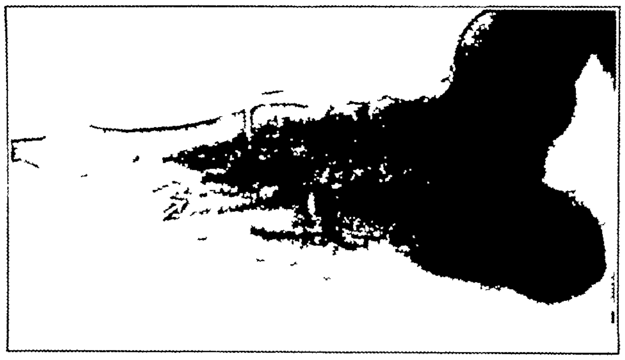

Fig. 7—Fracture of the third metatarsal plainly visible in the lateral view

Dr. Leo S Lucas Portland Ore I should like to emphasize further the importance of molding plaster in the longitudinal and anterior arches I think that in fractures of the metatarsal bones the plaster should be kept on for a suffici

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[5] Davis P A Fractures in Industry J A M A. **91** 695-698 (Sept. 8) 1928

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THE PSYCHIC FACTOR IN CARDIAC DISORDERS *

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NEW YORK

There are several impelling reasons for the selection of this topic for my contribution to this series of talks on subjects of special interest to the practitioner These may be stated briefly as first, the great prevalence of disorders of the heart having as their chief or only determining cause some purely emotional disturbance, second, the frequency with which such psychic disturbances are the result of some injudicious statement or action on the part of a physician—be he family practitioner, specialist or life insurance examiner, third, the fact that emotional reactions may play a very important part in the clinical picture presented by patients who have unmistakable evidences of organic heart disease, and, finally, the necessity, on the part of the practitioner, of a full and sympathetic understanding of these psychic factors if treatment is to be successful

It need hardly be explained, I am sure, that in this discussion of the interplay of reactions between the heart and the mind I speak entirely from the standpoint of an internist whose education has included no formal training in psychology or psychiatry and whose scanty knowledge of these subjects has been gained painfully in the hard school of experience But these deficiencies are shared, I believe, by most of my audience and perhaps we may understand each other the better for this common bond of ignorance

In its broader implications the title of this address should include not only a consideration of the influence of the mind in the production and maintenance of disorders of the heart but conversely the influence of disease of the heart in the production of mental disorders In the following discussion, however, I shall not attempt to include those frank psychoses, of exhaustive or toxic nature, which are occasionally seen as the accompaniments of the graver forms of organic heart disease, nor will I do more than mention here the teresting fact that women who, from childhood, have d a well compensated grade of mitral stenosis show usually not only distinct physical characteristics (undersize, delicate bony and muscular structure, poor fat panniculus) but also certain peculiarities in mental make-up, as seen especially in their great emotional nstability

W are all familiar with the fact that the emotions a direct influence on those bodily functions which are controlled by the vegetative nervous system and whose workings normally proceed without participation of the conscious mind One has but to recall their influence on the secretory functions, as exemplified in the flow of saliva and gastric juice called forth by the mere sight of appetizing food, their effect on the musculature of the gastro-intestinal tract, as shown by the vomiting excited by some revolting sight and by the diarrhea caused by fright or anxiety, their influence on the walls of the arteries as displayed in the flushing of embarrassment and the blanching of fear and anger The rare but well authenticated instances of jaundice following some violent emotion are to be explained probably as the result of spastic closure of the sphincter of Oddi Finally, the influence of the mind on the action of the heart is shown by the tachycardia, the palpitation, the premature beats and the precordial discomfort produced by sudden fright or violent anger For a full realization of the far-reaching influences of the emotions on the bodily functions, one should read Cannon's illuminating book "Bodily Changes in Pain, Hunger, Fear and Rage"

This influence of the emotions on the visceral functions is, obviously, exerted through the medium of the autonomic nervous system, since these organs are innervated only by that system, but the effects may be produced either by the direct action of the vegetative system on the respective organs or indirectly by its effect on the glands of internal secretion, such as the suprarenals

In approaching the subject of the psychic factor in cardiac disorders, it will be convenient to consider this factor first in relation to cardiac neuroses and later in connection with organic disease of the heart

THE PSYCHIC FACTOR IN CARDIAC NEUROSES

I shall not attempt a classification of the conditions commonly known as neuroses, but it may be helpful to distinguish between those disorders in which the symptoms are chiefly or wholly those of disturbed states of mind—the psychoneuroses—made up of morbid fears, apprehensions, anxieties, indecisions and depressions, and those in which the symptoms are due to disturbance of the functions of one or more of the internal organs—the so-called organ neuroses or the vegetative neuroses *In the one case the victim may have a* distressing fear of, say, heart disease without any actual symptoms referable to that organ In the other he may have obvious symptoms and signs of disturbance of the cardiac functions without, for a time at least, any conscious apprehension or fear When, however, the disorder has existed for some time it is usual to find both types of symptoms present and operating as a vicious circle, every appearance of a

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ad before the New York Academy of Medicine Dec. 6 1929 in es of lectures devoted to subjects of special interest to the oner

2 It demonstrates early or small lesions that are not visualized by the ordinary technic

3 It permits visualization of the anterior and posterior walls of the stomach and duodenum, as well as the marginal outline

4 It gives a truer picture of the size, shape and position of the stomach

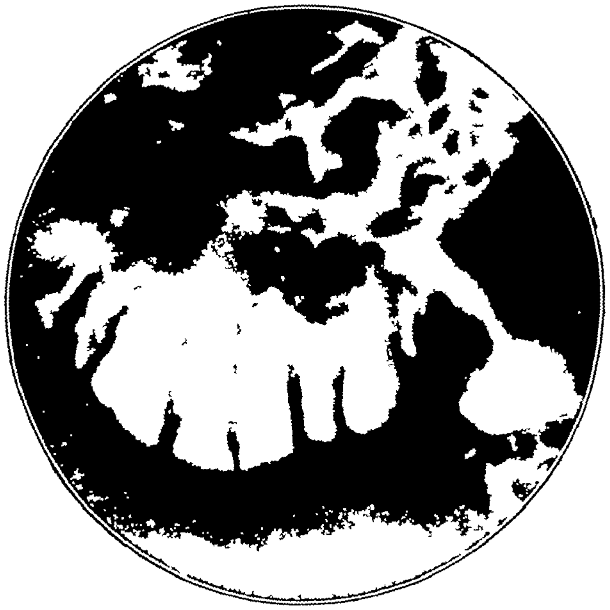

Fig 7 — A gastrojejunostomy showing the gastrojejunal ostium

5 It enables roentgenography under almost direct visualization

6 Less barium is used decreasing the danger of perforation lessening the discomfort of the patient and obviating largely the lower bowel disturbance frequently seen following gastro-intestinal roentgen examinations

7 When indicated complete filling and the indirect method can be combined with the direct

8 It obviates the necessity of numerous large roentgenograms, resulting in economy of material and lessened cost to the patient

CONCLUSIONS

1 The compression method increases the accuracy of gastro-duodenal roentgen diagnosis

2 It permits the demonstration of direct evidence of disease in a higher percentage of cases

3 It enables a more intelligent interpretation of the lesions present and a better understanding of the treatment indicated

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ABSTRACT OF DISCUSSION

Dr P M Hickey Ann Arbor Mich Williams of Boston in his book published in 1899 gave diagrams of some lesions of the stomach revealed by the test meal Of course he was antedated by Cannon in his famous physiologic experiments Cannon being I think, the first one in the world to use bismuth in the study of the gastro intestinal tract The great difficulty in clearness of investigations of the abdominal organs is the problem of scattered radiation that is as the direct rays strike the internal organs they give off secondary rays which tend to blur the plate There are two methods for the suppression of those first the limitation of the area examined by means of a cone or cylinder and second the use of a movable grid which was brought out first by Dr Buckey and afterward perfected by Dr Potter In this work the combination of the two methods has resulted in a somewhat more precise technic This was beautifully illustrated by Dr Boman s lantern slides It is unfortunate that in this country the manufacturers have not contributed to this work by following along the methods used by Åkerlund and Berg In fact, I was impelled, after I saw Berg s work, to make use of a crude home made piece of apparatus I quite agree with the author that the better the plates or films the more accurate the diagnosis It is necessary, however in looking at these films to relearn the art of interpretation of stomach films otherwise a little barium in one of the mucosal folds may be interpreted as a slight ulcer That, possibly is a theoretical objection but one has to work with a method for some time and become familiar with the appearance before one should give positive conclusions

Dr Robert R Newell San Francisco I am a little bold in accepting the invitation to discuss this paper because I have not used the compression technic on the partly filled stomach, as Dr Boman uses it Let me start out by admitting that my gastro-intestinal diagnosis is not satisfactorily precise I for one am ready to welcome any method that adds to the accuracy of the roentgenologic examination of the gastro intestinal tract I am one of Dr Boman s third group I would not do without roentgenoscopic examination and I would not do without film examination. I must have both It is my practice to see the patient first with the stomach empty and without any previous barium meal At this first visit I study the stomach and duodenum with an opaque meal Then in six hours I see the patient again to note the gastric emptying time Before seeing the patient at the six hour visit I study the films made at the first examination and then if any question arises (and a question often does arise) I can make a second immediate examination with another meal and do it more intelligently because I have in mind the specific questions which have been brought up in the case by a combination of roentgenoscopy and film study Dr Bowman s method examining the partially filled stomach under compression can well be considered as a supplementary method, to be added to the more usual examination with the stomach full I would not care to use it to the exclusion of the latter method The brilliant profile which one obtains by filling the stomach or duodenum must remain an important element in the complete examination.

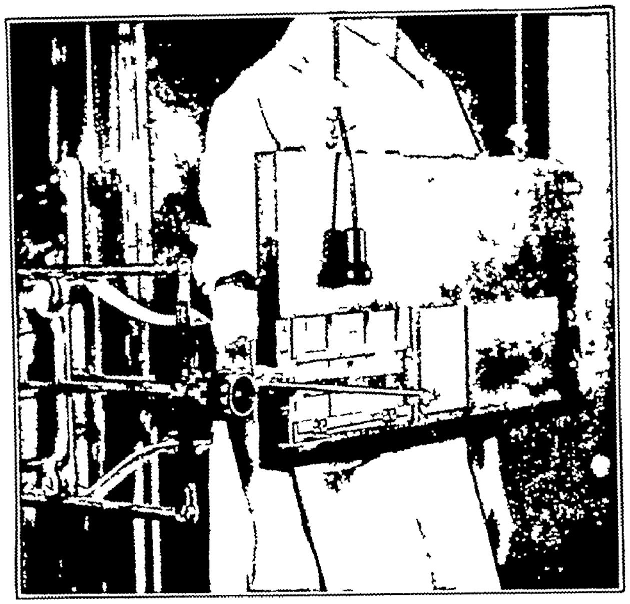

Fig 8 —Combined serialograph and compression device attached to the tube carrier of the combined fluoroscopic and roentgenographic unit

Dr. Martin G Vorhaus New York I should like to know how many of the cases demonstrated in the lantern slides were proved at operation or necropsy

Dr. George B Eusterman Rochest Minn
quarters has come the criticism that th
danger particularly in th

cardiac symptom serving to increase the mental agitation and this in turn increasing the tendency to cardiac symptoms

The psychic reaction to doubt concerning the integrity of the heart seems to be much more violent and profound than is the case with any of the other internal organs Most persons who would accept with considerable equanimity the knowledge that they had some disease of the liver or kidneys or lungs will have their morale sadly shaken by any evidence that the heart is not functioning properly In the minds of most laymen the thought of heart disease is still associated with the idea of sudden and unforeseen death This is perhaps the reason why the cardiac neuroses occupy such a prominent and important place in the list of organ neuroses

For the normal functioning of the organs under the control of the vegetative nervous system there is maintained a fine balance between the accelerator and the inhibitory mechanism by which such functions are carried on without participation of the conscious mind But all these functions are none the less, to some degree, susceptible to psychic influence Transient disturbances of this equilibrium occur, as has been pointed out, in normal individuals as a reaction to sudden psychic stimulation In the "neurotic" individual this response on the part of the vegetative nervous system seems grossly exaggerated and out of all proportion, in its severity or in its duration, to the psychogenic stimulus We are apt to think of such excessive reactions in terms of a "hypersensitive autonomic system" or of "autonomic imbalance" The question may be raised, however, in most such instances, whether the fault does not lie in a psychogenic stimulus which is excessive or unduly protracted rather than in an abnormally sensitive autonomic system

If one accepts the premise of a psychogenic basis for all the cardiac neuroses in which toxic or infectious causes may be excluded, then it must be admitted that such a psychic origin is sometimes so obscure and so deeply buried as at times to defy the most thorough search and questioning The stimulus may lie in some long past experience which has disappeared from the conscious mind and has sunk into the subcortical, automatic zone, where it remains only as an "organ memory" Nevertheless it may be stated with some confidence that the frequency with which a psychic cause is established will vary directly with the thoroughness and skill with which it is sought

But even though a careful search may fail to reveal a direct and obvious relationship between the cardiac symptoms and some definite psychic disturbance, it will rarely fail to disclose evidences of some instability of the nervous system as it relates either to the mind or to the autonomic mechanism It is surprising, in reviewing the history of patients with functional heart disturbances, to find how frequently one gets the story of some "nervous breakdown," either during the years of school or college life or in the course of some later period of stress In other patients without such a definite breakdown there will be indications of mental instability becoming apparent in the form of exaggerated introspection of great suggestibility, of morbid concern for health In still others there will be a history of other organ neuroses or clinical evidences of a disturbed autonomic nervous mechanism such as instability of vasomotor control, extreme lability of the pulse rate or blood pressure level, or marked sinus arrhythmia

When the psychogenic stimulus can be determined, it will usually be found to fall into one of the following four groups of causes

1 The statement of some physician or life insurance examiner that the heart shows some abnormality such as a murmur or irregularity of rhythm, or else the rejection of the applicant for life insurance on the score of some heart disturbance or of "high blood pressure" Sometimes it is a mere assumption on the part of the applicant himself that the heart must be diseased because two or three examiners were called in to listen to it In a person of the appropriate mental composition, the slightest suggestion that the heart is not intact may be enough to start a whole train of emotional reactions leading up to cardiac symptoms

2 The occurrence of some dramatic case of heart disease (perhaps with sudden death) among the relatives or friends of the patient

3 The appearance of some symptom which calls the attention of the patient to his heart and leads to a doubt as to its integrity This may be a sudden skip, a flutter or a twinge of pain, or may be merely what is regarded as undue palpitation or dyspnea after some special exertion Such disturbing symptoms are often first noticed during convalescence from an illness, such as an attack of grip, or they may appear as a result of the excessive use of tobacco or coffee

4 Some profound and protracted emotional disturbance, such as deep grief or prolonged anxiety, in which, however, there is at first no element of doubt concerning the state of the heart Much the most striking illustrations of the operation of this cause were seen during the war in the innumerable instances of that condition known variously as the irritable heart of soldiers, the effort syndrome or neurocirculatory asthenia As the result of the profound and long continued emotional disturbances incident to the process of volunteering or of being drafted into the army, such cases were encountered literally by the thousand and far outnumbered all the cases of organic heart disease found by the examining boards

A few illustrations may serve to emphasize the variety of these emotional causes

A man aged 22, a clerk seen in September, 1925, complained of shooting pains in the precordial region some shortness of breath, and insomnia He had never had any serious illness While in high school he had been very athletic and had had no symptoms In 1922 an insurance examiner told him that he had a heart murmur and should consult his physician This physician confirmed the finding and treated him by limiting his exercise, putting him on a diet and cautioning him against overexertion Up to that time he had felt perfectly well Soon after this he began to have pains in the left side of the chest and at times a feeling of breathlessness He grew very apprehensive, lost interest in everything except his condition had various nervous symptoms and could not sleep This state of things had continued for three years, during much of which time he had been unable to work A careful physical examination revealed no abnormalities whatever except a systolic murmur heard chiefly over the pulmonic area and having the usual features of an accidental murmur The process of restoring his confidence and his self-control was a slow and tedious one and it was three years more before he had entirely regained his health

An active and highly intelligent woman aged 50, a widow, was much distressed by frequent nocturnal attacks in which she would be awakened by violent palpitation and rapid heart action accompanied by flatulence and belching The attacks would last an hour or two and were so alarming that she usually was compelled to send for a physician These attacks had occurred at irregular intervals during the preceding ous samples of blood from the usual run of patients It seems to be accepted that creatinine, acetone and other bodies present in the blood filtrates, as well as dextrose, reduce picric acid while not affecting the copper solution of Folin and Wu Though the amount of this reduction may be negligible clinically, we decided to compare the two methods with stepped amounts of pure dextrose in distilled water Nor were we long in doubt as to the value of a statistical study With the first few determinations, rough preliminary curves showed waves in the Benedict method which we accounted for theoretically as due to variable mass action in the reducing power of the dextrose With increasing numbers of determinations these interesting waves were flattened out to the curve as shown in chart 1

All the procedures in this study were carried out in accordance with the directions given in the 1921 edition of Underhill's Manual of Selected Biochemical Methods

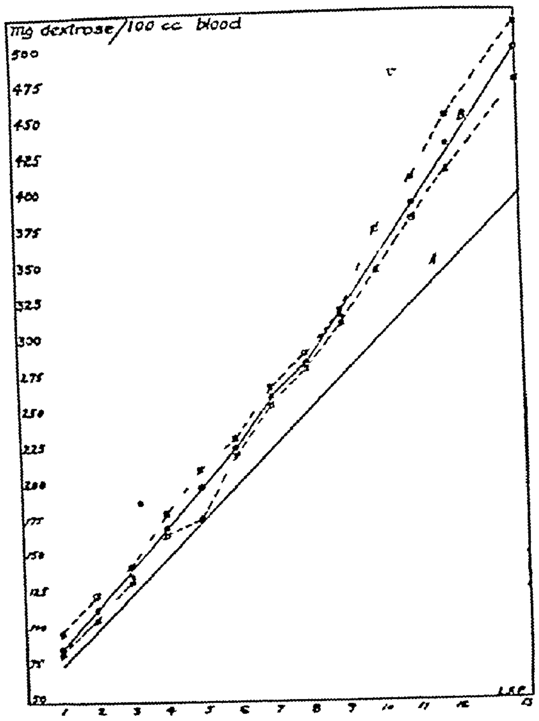

Chart 1 —Benedict modification of the Lewis Benedict method *A* actual dextrose content *B* experimental dextrose. In the charts the dotted lines represent maximum and minimum values

All the glass measuring pipets and flasks, other than the special tubes of the Folin type and the dilution tubes for the Benedict modification were certified and stamped as correct by the U S Bureau of Standards All chemicals were J T Baker C P Analyzed except the dextrose, which was the pure grade of the Eastman Kodak Company The dextrose was weighed accurately to 2 in the fourth decimal place Solutions were made with dextrose concentrations ranging from 75 to 400 mg per hundred cubic centimeters which were then analyzed according to the proper directions for each method Twelve determinations were made from each sugar concentration which totaled thirteen in each method, a final total of 156 analyses per method a number sufficient to warrant study and analysis of the results in the light of statistical mathematics

The colorimeter used was a Klett-Kober with artificial lighting, glass screen and independent milk glass reflectors The machine was checked for zero adjustment and standards were absolutely matched against one another and themselves every day in order that the reflectors might be in perfect adjustment All readings were made by a single individual, sufficient time being taken to rest the eyes in every determination and to get a color match satisfactory to both eyes

*Results of Blood Sugar Determinations with Various Procedures**

Concentration Mg per 100 Cc	Folin-Wu Unknowns	Mean Dextrose	Colorimeter Error E₀	Colorimeter Error E
	Low Standard Set at 15			
75	20.7 21.0 22.8 21.2, 21.9 22.1 22.2 22.0 22.0 21.5 22.5 21.4	67.8	±0.115	±0.398
100	14.6 15.0 15.0 14.8, 15.1 15.0 15.2 15.0 15.0 15.1 14.7 15.0	100.2	±0.033	±0.117
125	12.6 12.4 12.7 12.6 12.6 12.6, 12.6 12.0 12.6, 12.5 12.7 13.0	119.3	±0.045	±0.158
150	9.0 9.3 9.0 9.0 9.0 9.0 9.3 9.0 9.0 9.0 9.0 8.8	165.1	±0.027	±0.076
175	6.6, 6.6 6.7 6.5 6.6 6.7 6.5 6.6 6.4 6.6 6.5 6.6	225.2	±0.017	±0.059
	High Standard Set at 10			
200	9.2, 9.3 9.1 9.0 9.3 9.7 9.4 8.9 9.0 9.3 9.0 10.1	212.4	±0.072	±0.059
225	8.1 7.9 8.1 8.0 7.6 7.8 7.7 8.0 8.1 7.9 7.7 8.1	252.8	±0.035	±0.122
250	7.0 7.1 7.5 6.8 7.2 7.2, 7.3 7.0 7.5 7.0 7.0 7.2	279.8	±0.041	±0.143
275	6.5 6.3, 6.3 6.2, 6.2 6.1 6.0 6.0 6.2, 6.2, 6.6 6.3	320.0	±0.035	±0.120
300	5.6, 5.4 5.8 5.7 5.6 5.5 5.7 5.4 5.5 5.5 5.5 5.7	352.0	±0.025	±0.089
325	5.3 5.3, 5.4 5.6 5.1 5.1 5.4 5.3 5.1 5.4 5.0 5.3	370.8	±0.031	±0.117
350	5.0 4.8 4.9 4.9 4.8 4.6 4.7 4.7 4.9 4.9 4.9 4.6	415.8	±0.025	±0.098
400	3.9 4.0 4.1 4.1 4.0 4.1 4.2, 4.2, 4.0 4.0 4.4 3.9	426	±0.04	±0.139
	Benedict Modification of Lewis and Benedict			
	Dilution 12.5 Standard Set at 15			
75	15.2, 17.2, 16.8 17.7 17.1 17.9 18.1 17.3 17.9 17.5 17.2 17.3	87.2	±0.118	±0.514
100	12.2, 14.4 13.5 14.1 13.9 13.2, 13.7 13.5 13.9 14.0 13.4 13.5	115.6	±0.155	±0.45
125	11.2, 11.2, 10.8 10.7 10.5 10.9 11.0 11.2 11.2, 10.8 11.1 10.9	137.5	±0.048	±0.155
150	8.9 8.8 8.8 8.6 8.8 8.9 9.3 8.7 8.7 8.8 8.4 8.3	171.4	±0.049	±0.171
175	7.5 7.3 7.7 7.4 7.1 7.3 7.5 7.3, 7.8 8.5 8.5 7.5	197.3	±0.069	±0.307
	Dilution 25 Standard Set at 15			
200	13.6 13.5 13.2 12.9 13.4 13.2 13.5 13.4 13.3 13.3 13.2, 13.6	225.6	±0.014	±0.151
225	11.7 11.4 11.2 11.3 11.6, 11.5 11.6 11.7 11.5 11.5 11.4 11.6	260.8	±0.030	±0.103
250	10.5 10.3 10.4 10.5 10.7 10.5 10.5 10.5 10.7 10.6 10.7 10.7	284.4	±0.025	±0.089
275	9.6, 9.4 9.4 9.4 9.5 9.5 9.5 9.5 9.6 9.6 9.6 9.5	315.5	±0.015	±0.053
300	8.0 8.2, 8.1 8.3 8.5 8.2, 8.5 8.6, 8.2, 8.4 8.4 8.3	371.4	±0.035	±0.130
325	7.4 7.5 7.3 7.5 7.6 7.6 7.7 7.5, 7.8 7.7 7.5, 7.5	394.6	±0.027	±0.093
350	7.0 6.6 7.1 6.9 6.8 6.7 6.7 7.2, 6.7 6.8 6.9 7.0	431.8	±0.006	±0.123
400	5.8 5.9 5.9 6.1 6.0 6.3 5.9 6.2, 5.9 5.8 6.1 6.2	497.2	±0.025	±0.121

* The probable errors were calculated in all cases by the method of least squares Those interested in this detail are referred to Plane Surveying by Tracy The formulas involved are as follows

$E = 0.8453 \Sigma v/\sqrt{n(n-1)}$ which is the probable error for any single observation.

$E_0 = 0.8453 \Sigma v/n\sqrt{n-1}$ which is the probable error for the mean of all observations

v = difference of observation and mean.

0.8453 = a constant

n = number of observations

Checks on blood filtrates with added dextrose corresponding to these concentrations were not made in sufficient number to be statistically considered at this time eighteen months She had lost much weight because she feared to eat and she often stayed awake all night because of the dread of an attack if she should fall asleep She had never had an attack during the day or during her waking hours at night. What was more surprising was the fact that the attacks occurred only when she was occupying her house in the country and never when she was in her apartment in the city Physical examination did not reveal anything abnormal except for an occasional premature beat, and as it seemed important to learn more of the true nature of the attacks a nurse was supplied who was to be with her at night During the period that the nurse was in attendance, however, she was free from the nocturnal symptoms Then the fact was disclosed that a few months before the symptoms first appeared her husband had died during the night in a sudden heart seizure and, as their country house was some distance from the nearest village, she had been unable to get a physician until after he was dead She acknowledged that this experience was constantly in her mind when she was living in the country and it was not difficult to make her see the relationship between this state of mind and her nocturnal symptoms, which usually seemed to follow a nightmare. Soon after that the attacks ceased entirely

The wife of a physician, aged 35, complained of frequent attacks of irregular heart action and palpitation, with an increasing degree of breathlessness on exertion She had never had any illness except occasional attacks of tonsillitis as a child, but had always been rather apprehensive and easily disturbed nervously About two and a half years before, during a period of great mental stress, she noticed that her heart would sometimes pound and seem to skip a beat In spite of reassurance concerning her heart these symptoms returned from time to time and she grew increasingly apprehensive lest she have some serious heart disease Palpitation and irregularity became more and more frequent she found that any exercise such as dancing, which she had formerly enjoyed, would cause breathlessness and fatigue, and for a year she had been unable to look after her household and her children and had lived the life of an invalid The examination gave no indication of any abnormality of the heart or other organ and, under reassurance and encouragement, together with graduated exercises, the trouble slowly subsided and eventually disappeared

SYMPTOMS OF THE CARDIAC NEUROSES

Symptoms of the cardiac neuroses are predominantly of a subjective character, as is the case in most other forms of organ neurosis Such subjective symptoms include every possible variety of sensation from that of a slight fulness, soreness or "pressure" up to severe anginal pain with its characteristic localization and its radiation to the arm, neck or back Frequently the sensation relates to the heart beat and is described as fluttering, palpitation, pounding, or throbbing in the ears or temples A common form of unpleasant sensation is the single thump that follows a premature beat Occasionally the complaint is of a sensation as though the heart were not beating Another common symptom is the feeling of breathlessness, or of inability to take a satisfactory breath, without any actual dyspnea even on exertion All these subjective symptoms can of course be duplicated in organic disease of the heart, as well as in those functional disorders of toxic or infectious nature which cannot be classed among the neuroses in the stricter meaning of that term

Pain—When actual pain is present, its careful analysis will usually show evident differences from true anginal pain Rarely is it referred directly to the retrosternal region Usually its location is in the apical region or over the left half of the precordium Usually, too, it is made up of twinges of darting pain, and the steady, boring, constricting character of anginal pain is lacking There is seldom any close relationship between the pain and physical effort Indeed, the pain is much more apt to be felt when the patient is sitting quietly or is in bed than when walking But although the pain of the neuroses is ordinarily easily distinguishable from that seen in serious organic disease, it is by no means always so, and it cannot of itself be relied on to make the differential diagnosis between a neurosis and disease of the coronary vessels At times it may have all the characteristic features of true anginal pain and the recognition of its real nature must rest entirely on the other factors present Such cases have long been recognized, of course, under the names of pseudo-angina or vasomotor angina and they often present diagnostic problems of extreme difficulty

As an illustration of such difficulties in diagnosis the following case may be cited

A man, aged 48, seen in 1928 because of frequent attacks of anginal pain, stated that he had had his first attack of pain in 1922 at a time when he was much fatigued and under a good deal of mental strain. In that attack the pain began as a severe ache, felt at the lower part of the sternum and later radiating down both arms to the elbows The discomfort lasted six or eight hours He was seen by an able internist, who associated it with an attack of influenza in 1918 and put the patient to bed for several weeks After that there was no further illness until the spring of 1928 (an interval of six years), when during another period of strain and worry he became faint and dizzy noted that his heart was beating rapidly, and felt 'hysterical" The rapid heart action lasted some hours and he was put to bed for several days After an interval of three months he was awakened by another attack of retrosternal pain which radiated to his right shoulder and arm Since that time he had had frequent similar attacks, coming on at different times of the day and varying greatly in severity and duration The pain was felt sometimes while walking, frequently after eating, and occasionally at night It usually began behind the sternum and radiated to the right arm but occasionally it was felt first in the elbow With the pain there was a feeling of constriction and weight and during severe attacks some shortness of breath

Examination of the heart yielded normal observations except for an occasional premature beat. The orthodiagram showed a rather small, vertical heart and a normal arch shadow The radial arteries were slightly thickened, the pulse rate was slow, and marked vasomotor instability was shown by the intermittent flushing of the face and neck The electrocardiogram gave a normal tracing except for the occasional ventricular premature beats

The patient himself was evidently a nervous, highly sensitive man who felt the weight of his rather heavy business and family responsibilities but no obvious psychic relationship to his disorder was disclosed

Although there were many factors that suggested that the trouble did not have a structural basis, the character of the attacks of pain was such as to make one hesitate to ascribe the disorder wholly to emotional disturbances The patient was later placed in the hands of a skilful psychiatrist, who became convinced that the trouble was purely an anxiety neurosis and was able to make various helpful readjustments in the patient's life. For the past year he has been entirely free from his old symptoms and has lived a normal, active life As it is now more than eight years since his first attack of pain, the psychogenic nature of the trouble seems established

Objective Symptoms—A change in the heart rate is much the commonest of these symptoms Such a change is almost always in the direction of acceleration, and tachycardia in response to any emotional disturbance is especially characteristic Nevertheless a pronounced slowing of the heart rate as the result of profound emotion does undoubtedly occur With the tachycardia there is often violent heart action with throbbing of the whole precordium, such as occurs normally in fright or anger Premature beats of the ventricular type are frequently encountered even when the influence of such toxic agents as tobacco and coffee can be excluded Evidences of excessive vasomotor lability are present in most patients in the form of ready flushing in response to even slight emotional changes

In the special type of neurosis known as the irritable heart of soldiers many of the symptoms already mentioned, both subjective and objective, are joined with certain other symptoms to form a striking and characteristic syndrome Tachycardia, palpitation, throbbing arteries, precordial pain, fatigue and dyspnea on slight exertion, tremor, sweating and clammy, cyanotic hands combine to make a clinical picture which, once seen, can never be forgotten

THE PSYCHIC FACTOR IN ORGANIC HEART DISEASE

It is not to be supposed that organic heart disease is found only in individuals with a stable mind and nervous system, and when it appears in persons whose mental make-up predisposes them to apprehensions and fears, one may expect to find evidences of this tendency in the appearance of symptoms which cannot reasonably be ascribed to the organic disease present In such cases one may be confronted with a wide range of symptoms, chiefly subjective, which lie outside the legitimate manifestations of the existing organic disease When the structural disease is itself causing severe or distressing symptoms the neurotic symptoms, if present at all, are apt to be relatively unimportant. It is in the milder forms of heart disease, with few or no real symptoms, that the emotional reactions tend to occupy the foreground of the picture and demand serious consideration On their proper evaluation by the physician may rest the entire structure of successful treatment This differentiation between the symptoms which are the legitimate result of the existing organic disease and those which are merely the expression of the associated psychic upheaval demands the utmost in skill, judgment and experience on the part of the physician He must know from experience just what is to be expected in the way of symptoms from the type and grade of the organic lesions present in order to recognize that certain of the symptoms have no direct relation to the somatic disease

This association of organic disease with symptoms of a purely neurotic nature is encountered in patients of almost all ages One sees it in older children with rheumatic heart disease who have been taught, usually by an overanxious mother, that all physical effort is to be avoided, it is found frequently in neurotic women with long-standing but relatively mild mitral stenosis, and it is by no means uncommon in persons in middle life who are oppressed by the knowledge that they suffer from "high blood pressure" A single instance will serve to illustrate this association

A married woman aged 36 while on a visit to the city had a sudden attack of faintness and weakness so severe as to require the immediate services of a physician The symptoms continued for two days and were accompanied by great mental agitation and by the constant fear that she was about to die The physician in attendance recognized that she had a valvular lesion but could find no satisfactory explanation for her sudden and alarming symptoms She was seen in consultation on the second day because of the persistence of these symptoms She presented the characteristic signs of mitral stenosis, but the heart was only slightly enlarged, its action was regular and not unduly rapid and there was complete absence of all the usual signs of disturbed compensation From her husband it was learned that for many years she had known that she had a "heart murmur," but she had always been very athletic and had played tennis and taken other active exercise without any discomfort whatever There had been no symptoms at the time of the birth of her two children During the preceding year or two, however, she had had a number of attacks similar to the present one, always accompanied by great psychic disturbance and by the fear of death Between the attacks she had been perfectly well These attacks, her husband believed, were the result of anxiety concerning her heart trouble, as during this time her home physician had reminded her frequently that she had heart trouble and should be cautious about exerting herself It required much persuasion and reassurance to induce the patient to leave her bed and return to her home, but the trip was made without difficulty and at last accounts she was leading her normal, active life and had regained some of her lost confidence.

What has been said thus far concerning the psychic factor in organic disease of the heart has related to the appearance of neurotic symptoms as the result of anxiety caused by a knowledge of the existence of heart disease I will now call attention to the part which profound and protracted emotional disturbances may sometimes play in aggravating the existing heart damage and in producing serious cardiac symptoms Physicians are much too prone to regard physical overexertion as the most serious hazard to which cardiac patients are exposed and to fail to give proper weight to the potentialities for harm that reside in violent psychic stimuli

The following dramatic case history will illustrate this danger better than any description I can give

A man, aged 45, a painter by trade, was brought to the New York Hospital by ambulance, Oct 7 1929, with every evidence of grave heart disease While riding in a street car he had had a sudden attack of severe dyspnea with thoracic pain and oppression and had fainted On arrival at the hospital he was still dyspneic and cyanotic and was raising frothy, bloody sputum Physical examination showed a greatly enlarged heart, with all the cardiac and vascular signs of a severe grade of aortic insufficiency with failure of compensation The heart was beating regularly and at a rate of 44 to the minute and an electrocardiogram showed complete heart block. When the patient had improved sufficiently to give a detailed history of his trouble, it was learned that at the age of 18 he had had gonorrhea and about the same time some arthritic symptoms which were ascribed to the venereal infection He had had a mild painter's colic in 1916 and influenza in 1918 Apart from this he had always been well About seven years before, during an examination for life insurance, he had been told that he had a 'leaking valve," but this had given him no symptoms whatever and he had continued at his trade and had been perfectly well until Aug 25, 1929, when he had had a sudden attack of dyspnea and precordial pain This abrupt onset of symptoms in one who had evidently had a valvular lesion for many years led to further questioning in the course of which the following tragic story was brought to light His wife had died in 1916 and since that time he had centered his affections on his son, who had become very close and dear to him August 15, the boy had been killed in an automobile accident Following the death of his son the patient became melancholy and morose. On the evening of August 25, while brooding over his loss, he had had the sudden attack of dyspnea described Following this there were frequent attacks of dyspnea at night but during the day while he was busy at his work he felt pretty well October 7, while riding in the car and thinking of his son, he had the severe attack which brought him to the hospital As he improved slowly, his heart resumed a sinus rhythm but the auriculoventricular conduction time remained extremely long (0 64 second) In view of the finding of a heart murmur seven years before of the absence of stigmas of syphilis and of a negative Wassermann reaction in both the blood and the spinal fluid, it seemed probable that the aortic insufficiency was of rheumatic origin. Whether the heart block was of long standing or whether it was the result of vagus stimulation as a part of the patient's profound emotional reactions, it is impossible to say

TREATMENT

It is in connection with the treatment of the psychic aspects of cardiac disorders that one feels most keenly one's deficiencies in psychiatric training Then it is that one must bring to bear on the problem all that has been gathered of experience and sympathetic insight into the obscure and tangled processes of the human mind At times it is much easier to recognize the importance of these psychic factors than to know how best to deal with them

In many instances the problem is simple and a tactful explanation of the situation and reassurance may be all that is needed At other times the therapeutic problem is difficult and complicated and clearly calls for the assistance of a trained and experienced psychiatrist Generally, however, it falls to the lot of the family physician to deal with such patients, and if he has had the insight to recognize the significance of the emotional factor he will usually be found to possess the judgment and good sense necessary to effect the cure Tact and common sense will go far toward compensating for the lack of psychiatric technic

A word should be said first concerning prophylaxis Obviously the fundamental difficulty in a patient with a cardiac neurosis lies in his personality and his mental composition, and those ingrained characteristics one can hardly hope to alter materially But this fact makes it all the most important that as physicians we exercise great care to avoid supplying such an unstable individual with any suggestion that may serve to crystallize his fluid anxieties and center them on his heart

If in the course of health or insurance examinations some unimportant cardiac anomaly is noted by the examiner, it is often wise to avoid mention of it, or, if it seems necessary to apprise the patient of it, the matter should be presented to him in such a way that it will carry with it reassurance and will put his mind at rest concerning its significance Often it is necessary also to caution the anxious parents of children with the milder forms of heart disease concerning the harmful effects of too constant reminders to the child that his heart is crippled and that he is not like other children Such an attitude may well lead to psychic scars more serious and disabling than those of the heart valves

Coming now to the matter of treatment, usually the first problem to be faced is that of acquainting the patient with the fact that his symptoms are due to emotional causes rather than to disease of the heart itself One might expect that such knowledge would come to him as a great relief, and frequently this is the case But by many patients the intimation that the heart is normal and that the symptoms have a psychic origin is interpreted as meaning that the symptoms are 'imaginary," and the first reaction to such a disclosure is apt to be one of strong resentment Such a reaction must be prevented at any cost, for, if it occurs, one's usefulness with that patient is ended In no other condition perhaps is complete faith in the judgment and wisdom of the physician so essential to success in treatment The patient's understanding of the true character of his complaint must not be gained at the expense of his self-respect If the necessary time and trouble are taken, it is usually not difficult to convince the patient that one realizes that his pain, palpitation and dyspnea are no less real and disturbing because they are brought about by agencies outside the heart itself, the really important difference being only that in his case the symptoms are curable whereas if they were the result of organic heart disease they might not be Such a discussion should of course be preceded by a thorough and complete physical examination Often it is wise to supplement this by instrumental examinations as well in order that, when the statement is made that the heart is not diseased, it may be backed up by as powerful an array of facts as possible The casual announcement after a hasty and superficial examination that "there is nothing the matter with the heart" will almost certainly fail to carry conviction

If the patient can be persuaded to accept without resentment the idea that his symptoms are of "nervous' origin, the battle is half won From that point on the treatment consists chiefly in the liberal application of the two most generally effective remedies in the physician's armamentarium—reassurance and encouragement Chiefly on their skilful use will depend the promptness and completeness of the recovery But the reassurance must not be simply that of the spoken word The patient must be shown how to reassure himself by a demonstration that his cardiac symptoms are made better rather than worse by the exercise and effort which hitherto he may have feared to undertake To assure a patient that his heart is normal and at the same time to impose various restrictions as to its use is a contradiction which he will be the first to recognize

Exercise of some form is usually an essential part of treatment It serves the double purpose of demonstrating to the patient that his heart is capable of much more than he supposed and of rendering the heart less irritable and less ready to respond to the psychic stimuli The form of exercise to be selected will depend on the special requirements and circumstances of the individual patient In one case it may be some outdoor sport, such as golf or even tennis, which combines recreation with muscular development In another it may be graded room-exercises or gymnasium work under the supervision of a trainer Whatever the type of exercise selected, it must be carried out regularly and persistently and must of course be graduated carefully to suit the capacity of the patient

As for the use of drugs, it is my judgment that they should be avoided unless there is a clear and imperative reason for their administration The encouraging effect on the patient of being told that he does not need medicine usually far outweighs any transient benefit that may be gained from its use If at the outset it seems important to utilize the sedative action of such drugs as phenobarbital and the bromides, these should be discontinued just as soon as the urgent need for them has passed As for drugs such as digitalis and quinidine, which are known to be used for their effects on the heart, they can do nothing but harm No intelligent patient can possibly be persuaded that his heart is sound when at the same time he is asked to take digitalis

In deciding on the advisability of such measures as rest in bed, baths and massage, the guiding principle should be the probable effect of such procedures on the mind of the patient The chief objection to them is that they so often serve as a constant reminder to him that he is not well, and this mental effect may nullify any physical benefit that might otherwise be derived from them Much the same may be said concerning the interdiction of tobacco and coffee Whenever it is known that the use of either of these substances is excessive and is contributing to the neurotic symptoms, they should of course be forbidden, but when there is no reason to think that the smoking or the coffee drinking plays any part in the production of the symptoms it is usually wise to permit the continuance of the habit so long as it can be kept within bounds Every liberty of this sort that can safely be given will have the effect on the patient of encouraging him and of persuading him that he cannot be seriously ill

From what has been said concerning treatment it must be apparent that, in my judgment at least, the management of patients with cardiac neuroses belongs essentially to the realm of psychotherapy The details of such treatment will of course vary with the character of the individual patient and with the predilections of the physician If the latter will but keep in mind the psychic basis of the neurotic symptoms and the need of treating the mind of his patient rather than the symptoms themselves, and if he can call to his aid a modicum of tact, common sense and optimism, he is likely to be rewarded by results quite as brilliant and as satisfying as are ever obtained in any field of internal medicine

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THE NONSPECIFIC TREATMENT OF NEUROSYPHILIS

FIFTH ANNUAL REPORT *

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In this report we review the status of a group of patients with neurosyphilis who were given fever therapy and who have now been under observation from three to five years We will include, also, further observations on a smaller group of patients who were treated with nonspecific typhoid vaccine and who have been observed for two years

Of the 213 patients treated between June, 1924, and June 1926, 179 are available for this study The remaining thirty-four have not been heard from for more than two years One hundred of these patients, at the time they were inoculated with *Plasmodium vivax*, according to the suggestions of Wagner-Jauregg,[1] had the early signs of paresis, although in a few the disease had progressed far enough to require institutional care The majority had been under treatment for parenchymatous neurosyphilis for several years, long enough for the observation that the advance in the clinical signs and the absence of serologic response indicated the development of paresis In all the cases there were varying degrees of personality changes, loss of memory, tremors and objective neurologic changes None, however, were of the advanced or vegetating type of paresis

Of the 100 patients, the condition of thirty-eight is still in complete remission, thirty-one have been improved by some method of treatment, seventeen did not derive any benefit or were made worse, and fourteen are dead Table 1 shows the annual clinical status of the patients with paresis treated during the last five years There are five patients of the original group of fifty-seven who were in remission last year and are now regarded as "improved" They have shown slow but steady mental deterioration during the last two years and have had difficulty in maintaining their positions They are not troublesome and have fair insight but poor *coordination and lack of initiative* In previous reports attention has been called to the criteria that we maintained in the estimation of clinical remissions, basing the deductions solely on the economic status of the patient as a result of the fever therapy Even though a patient derived material improvement, if he was unable to support himself or his family he was not graded as in remission Of the fourteen patients reported as being dead, five died directly as a result of the malaria and three as a result of paresis, the remaining six deaths were the result of accidents, suicide and other diseases

Table 1—*Annual Clinical Status of One Hundred Patients With Paresis Observed from Two to Five Years*

	1924	1925	1926	1927	1928
In remission per cent	Not appraised	38	49	41	38
Improvement per cent	Not appraised	15	17	25	31
No change per cent	Not appraised	25	11	11	17
Deaths during the year	Not appraised	7	1	2	4

The serologic reports in this series of patients with paresis are equally encouraging (table 2) In sixty of the group the spinal fluid has been reexamined during the last six months and has been found to be completely negative in all factors in 52 per cent of the cases In an additional 30 per cent the spinal fluid reactions have been materially improved, although a weakly positive Wassermann reaction and a positive Nonne reaction persist, the cell count is well within normal limits

The study of the serologic reactions of thirty-eight of the forty patients who were in complete remission showed that twenty-eight (73 per cent) now have completely negative reactions of the spinal fluid and blood In all cases the serologic tests on the blood were done by both the Kolmer technic and the Kahn technic

The results in the treatment of patients with taboparesis have not been so satisfactory Of the thirteen patients in this group, four are in complete remission, three are somewhat improved, and six are dead The poor results in this group are in a measure attributable to the fact that these patients had been under treatment for tabes dorsalis, both in the clinic and elsewhere, for many years, but none the less the disease continued to progress clinically The treatment by malaria was given as a last resort In our experience these are unsatisfactory circumstances in which to use fever therapy because the progressive downhill course is frequently accelerated by the treatment The advanced parenchymatous changes and the general debility associated with them will not withstand malaria Their counterpart is seen in the patient with advanced signs of paresis

Table 2—*Results of Examination of Spinal Fluid in Sixty of the One Hundred Cases of Paresis*

	1924	1925	1926	1927	1928
Reversed to negative per cent	Not estimated	Not estimated	21	57	73
Improvement per cent	Not estimated	Not estimated	24	33	11
No change, per cent	Not estimated	Not estimated	55	10	11

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* From the Section on Dermatology and Syphilology the Mayo Clinic.

* Read before the Section on Nervous and Mental Diseases at the Eightieth Annual Session of the American Medical Association Portland Ore July 10 1929

[1] Wagner Jauregg J Malariatherapie Wien klin Wchnschr **41** 672 674 (May 10) 1928

On the other hand, the group of patients with neurosyphilis classified as paresis sine paresi, or asymptomatic paresis, manifested satisfactory results Included in this group are patients who have been under treatment for parenchymatous or interstitial neurosyphilis with the use of intravenous, intramuscular and intraspinal measures for periods varying from one to three years In spite of the treatment there was evidence of clinical progression and failing acuity, but none of them showed enough evidence of mental impairment to warrant a diagnosis of paresis The reactions of the spinal fluid had remained persistently positive, with a persistent zone 1 or paretic type of colloidal benzoin and colloidal gold curve In this group are included also the patients to whom the term "chronic relapser" has been applied because the spinal fluid reverts to normal while the patient is under continued treatment, only to relapse with marked pleocytosis and a persistent zone 1 or paretic gold or benzoin curve when the patient is given a rest period Of these twenty-two patients, ten have manifested complete reversal of serologic reactions to negative, and decided clinical improvement has been noted, six (20 per cent) have improved, two have died, and four have not derived benefit or were made worse

The asymptomatic neurosyphilitic patient is the ideal subject for fever therapy The distinguishing features between cases of asymptomatic neurosyphilis and those of paresis sine paresi are not always clear-cut In the former group the reactions of the spinal fluid are positive but the patient does not show objective signs of neurosyphilis, whereas in the latter group the early clinical signs and the persistent serologic reactions of the paretic type are not influenced by treatment The results in this asymptomatic group can be determined only by serologic changes Of the ten patients who have been under observation now for more than three years, seven have experienced complete reversal to normal of all the factors in the spinal fluid In three there has been limited improvement in the serologic reactions In a previous communication, one of us [2] called attention to the fact that this asymptomatic neurosyphilitic group offers the ideal field for fever therapy Continued observation seems to confirm this impression

Table 3—*First and Second Courses of Antisyphilitic Therapy*

Date	Original Arsphenamine	Mercury
9/20/26 to 10/15/26	6 injections (3 1 grams)	16 injections of succinimide (2⅔ grains)
10/15/26 to 11/20/26		40 inunctions
11/26/26 to 12/31/26	6 injections (2.6 grams)	18 injections of succinimide (3 grains)

As an example of the value of treatment by malaria in the treatment of neurosyphilis, associated with acute syphilis of the meningeal type, the following case history is cited

In September, 1926, an unmarried woman, aged 21, presented herself at the Mayo Clinic with secondary manifestations of syphilis in the form of grouped follicular lesions and mucous patches from which the dark-field examination was positive for *Spirochaeta pallida* The Wassermann reaction of the blood was strongly positive. Antisyphilitic treatment was started at once and four courses of intravenous arsphenamine, intramuscular injections of mercuric succinimide and mercury inunctions were given as indicated in tables 3 and 4

During the second course of arsphenamine the patient complained of persistent headaches, but examination of the spinal fluid at this time revealed a negative Wassermann reaction, a negative Nonne reaction, and two cells The Wassermann reaction of the blood was negative at the end of the second course

The patient did not return for the fourth course of arsphenamine at the stated time but allowed four months to elapse before she returned. During this time she took twenty-four mercury rubs She returned, Aug 16 1927, complaining particularly of persistent occipital headaches examination of the spinal fluid showed a strongly positive Wassermann reaction, a positive Nonne reaction, 9 cells, and a colloidal benzoin curve of 012103332000000 The Wassermann reaction of the blood had also relapsed to total inhibition after it had been negative for eight months The fourth course of combined arsphenamine and mercury consisting of six injections of original arsphenamine (2 7 Gm.) and twenty injections of mercuric succinimide (3⅓ grains or 0.22 Gm.), was given between August 25 and September 29 The patient returned two months after the completion of this course because the headaches persisted Tests of the blood and spinal fluid were still strongly positive, and there was an increase in pleocytosis to 49 lymphocytes Accordingly, she was inoculated Jan 10 1928, with *Plasmodium vivax* and allowed to run a course of malaria consisting of twelve chills The results of two examinations of the spinal fluid and blood since that time are given in table 5

Table 4—*Third and Fourth Courses of Treatment*

Date	Original Arsphenamine	Mercury
1/10/27 to 2/20/27		24 inunctions
3/ 4/27 to 4/ 8/27	6 injections (2.4 grams)	15 injections of succinimide (2¼ grains)
6/10/27 to 7/ 4/27		24 inunctions
8/25/27 to 9/29/27	6 injections (2.7 grams)	20 injections of succinimide (3⅓ grams)

Antisyphilitic treatment has not been given since the malaria, and there has not been a return of symptoms

From the observations in this and other similar cases, we now recommend the use of fever therapy when prolonged treatment with the arsphenamines and mercury or bismuth which was started during the early manifestations of acute syphilis has failed to control the unfavorable progress of the diseases as manifested by the condition of the spinal fluid Patients with acute syphilis who have neurorecurrences following a supposedly satisfactory course of treatment may also be candidates for fever therapy We do not mean to imply by this that all patients with acute syphilis should be treated in this manner, but it is a most satisfactory method of treatment when measures used as a routine fail to control the progressive development of neurosyphilis during the early course of the disease The recognition of such progress demands three or four examinations of the spinal fluid during the first two years of the disease

Table 5—*Reaction of Blood and Spinal Fluid After Malaria*

	Spinal Fluid		Blood
7/18/28	Wassermann reaction negative Nonne reaction negative 7 cells colloidal benzoin curve 000003331000000	7/18/28	Wassermann reaction negative
7/17/29	Wassermann reaction negative Nonne reaction negative 3 cells colloidal benzoin curve 000033332000000	5/16/29	Wassermann reaction negative

The patients with tabes dorsalis and its varying complications who were treated by malaria have not maintained the improvement that their early observation suggested In this group are thirty-four patients with tabes dorsalis, of whom twelve had gastric crises, fifteen optic atrophy, three persistent leg pains and four the uncomplicated progressive type of tabes dorsalis One of the patients with gastric crises has been completely relieved for three and a half years Five (41 per cent) have noted a decrease in the severity of the attacks and an increase in the interval between them The remainder have not derived any benefit Of the three patients with persistent leg pains, one has been completely relieved and two have not improved The patients with optic atrophy have practically not derived any benefit, the majority continuing to lose vision slowly and progressively One of the cases of uncomplicated tabes dorsalis has shown complete reversal of serologic reactions to negative, with general tonic improvement paralleling it It is obvious that the results in the tabetic type of parenchymatous neurosyphilis, in our experience, have fallen far short of the results obtained in the paretic type.

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[2] O Leary P A. Treatment of Neurosyphilis by Malaria Serologic Results and Comparison with Treatment by Typhoid Vaccine J A. M A. 91 543 545 (Aug 25) 1928

In reporting these results in the various types of parenchymatous neurosyphilis we have commented rather freely on the results of the serologic tests However, it is not our belief that the study of the spinal fluid and the blood affords a true index of the value of the remedy In several cases an outstanding clinical remission of four years' duration has not been paralleled by a significant serologic change The converse also has been noted, wherein complete reversal of the serologic reactions to negative has not been attended with clinical improvement

TREATMENT BY TYPHOID VACCINE

In June, 1926, we started to use typhoid vaccine intravenously in an effort to reactivate the chills and fever of patients in whom the malaria had aborted after a short and incomplete course Later, we used the typhoid vaccine for patients in whom we were unable to produce malaria and in those in whom malaria had aborted following a few fever bouts Kunde, Hall and Gerty[3] first reported on this form of treatment in October, 1927 Forty-eight patients with paresis have been treated in the clinic by this method and observed for from one to two years Our experience with treatment by malaria makes us hesitate to pass judgment on the treatment by typhoid vaccine at this time, particularly because when we first used typhoid vaccine we failed to produce enough paroxysms and likewise hesitated to use sufficiently large doses

From a study of this group it is obvious that to obtain satisfactory results from treatment by typhoid vaccine a larger series of chills must be given than with malaria and that increasingly larger doses of the vaccine are necessary to produce satisfactory reactions However, malaria and typhoid vaccine have in common the fact that in the majority of cases of paresis high fever with marked constitutional reaction seems necessary to produce satisfactory remissions The injections may be given every other day, from twenty to twenty-five injections to constitute a course, starting with 25 000,000 bacilli injected intravenously, and increasing the dose, depending on the patient's tolerance to the typhoid vaccine, however, usually intolerance can be overcome by giving much larger doses The complications, although not so numerous, resemble those of malaria in a less pronounced manner Varying degrees of jaundice, hepatitis, nephritis and myocarditis have been noted However, severe dementia has not been encountered even in association with high fever A series of patients with other types of neurosyphilis also has been treated, but as yet the number is not large enough to warrant deductions

Treatment by typhoid vaccine has several advantages over treatment by malaria The occasional patients with resistant neurosyphilis may be treated with vaccine at home Deaths have not occurred in our series, complications have been fewer and less serious, and it seems that an institution organized for the care of such patients is not necessary for such treatment On the other hand, it should be borne in mind that the therapeutic results following treatment by typhoid vaccine are decidedly less marked than those following treatment by malaria, as the remissions are slower and less pronounced in developing, and there are decidedly fewer remissions

CONCLUSIONS

From June, 1924, until April, 1929, we treated 509 patients by malaria An additional 140 patients were inoculated with *Plasmodium vivax*, but malaria did not develop The patients who have shown outstanding results are those with early manifestations of paresis, those with paresis sine paresi, and those with asymptomatic neurosyphilis who failed to show response to intravenous medication Of the original twenty-four patients treated by malaria and reported on in 1925, ten are still in complete remission, five have not shown improvement or have steadily progressed, four are dead, and five have not been heard from for more than two years

The serologic reactions, although of interest, are not always of prognostic significance, and an effort to evaluate the method of treatment from the serologic reactions alone may be misleading The objective signs of parenchymatous neurosyphilis which are the result of a destructive process in the nervous system are not materially influenced by this form of treatment On the other hand, the more meningeal the degree of the involvement, the better the results

Several patients who showed obvious clinical signs of paresis but who were in complete remission for about two years following treatment by malaria have manifested signs of slow but steady mental deterioration The evidence from this study and a review of the literature indicate that the life expectancy of patients with paresis is increased by treatment with malaria, even though complete remission does not develop Notwithstanding opinions to the contrary, results of this type are not a contraindication to the method

Treatment by typhoid vaccine may be substituted if treatment by malaria is not possible, although the therapeutic remissions in our experience have been less frequent and less pronounced

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[3] Kunde, M M, Hall G W and Gerty F J General Paralysis Effect of Nonspecific Protein Therapy on Blood and Spinal Fluid J A M A 89 1304-1308 (Oct. 15) 1927

The Smoke Problem —Why should we be interested in the smoke problem? What harm does it do? The harm is so well understood that it should not be the subject of controversy First, it is injurious to health. It affects the eyes, nose and throat and air sinuses, lowering the resistance of these parts to disease. It affects the respiratory tract and the bronchial tubes That the soot reaches these tubes is readily seen by the blackish mucus coughed up in the morning In the lungs themselves the carbon particles become embedded, and in time the lungs change their natural pink to a black color The irritation of the smoke and particles produces scar tissue and in time interferes with the normal action of the lungs In addition to its effect on health, there is loss of sunlight with its violet rays, due to the screening of the sun by the smoke—particularly so on foggy days —Darlington, Thomas Smoke, *New York State J Med*, Nov 15, 1929

ANTISYPHILITIC TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM *

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The treatment of syphilis of the central nervous system belongs to the everyday practice of the neuropsychiatrist. In this paper I shall give the experiences and results obtained with combined antisyphilitic treatment in the Wisconsin Psychiatric Institute at the University of Wisconsin. An analysis of the enormous literature dealing critically with clinical, serologic and research problems of neurosyphilis shows that there are few diseases more diversely treated and that the trend of syphilotherapy is unfortunately toward simplification, which is to be deplored. It is not known whether the antisyphilitic agents now in use are spirocheticidal or whether they primarily change the lipoid metabolism by an omnicellular hyperactivity with unknown colloidal changes by which the bodily resistance becomes increased and the activity of the spirochetes becomes reduced. Nearly all investigators agree that malarial inoculation is the treatment of choice for arsenical-resistant cases of neurosyphilis, especially in paresis. It is felt that, during convalescence from malaria, complemental therapy consisting of arsenicals, mercury and bismuth results in more frequent remissions. The results obtained with malaria are better than those reported from other antisyphilitic agents. The enthusiasm for malaria and other nonspecific methods should not lead to the discard of specific remedies.

Antisyphilitic therapy necessitates a knowledge of the biologic action of the drugs to be employed as well as their indications and reactions, which should be benign and controllable. Neurosyphilis cannot be treated by any routine procedure and cannot be standardized as yet. Each case presents a problem in itself. Only after a careful clinical and serologic investigation should the therapy be outlined, with substitutions if the drug of choice is not successful after a certain period of time. An individual adjustment is necessary depending on the constitution, the general health, the age and the sex of the patient. A robust individual can be treated more energetically than an emaciated one. The acute meningovascular case must be differently attacked therapeutically from the case of congenital neurosyphilis. Likewise the duration of treatment should be extended over variable periods and should be followed by rest periods depending on the progress of the disease.

INTRASPINAL THERAPY

In spite of many theoretical objections to intraspinal therapy, whether the Swift-Ellis or Gennerich method is employed, it remains a fact that in some resistant cases of paresis and tabes there is great improvement, while in other cases it fails utterly. The great sensibility of the brain and cord resulting from the metasyphilitic involvement necessitates extreme precaution. As a former student of Gennerich I have studied and employed this method carefully and have obtained satisfactory results in cases in which combined therapy failed to relieve pain or to change the serologic reaction. It should be, in my opinion, the last therapeutic attack. It is the treatment of choice in cases of rapidly advancing meningeal involvement with severe crises, optic atrophy and increased intracranial pressure and in those cases which present an intolerance to intravenous injections of arsphenamine. These are indications for the endolumbar therapy. The intraspinal injection of neoarsphenamine offers better results than the Swift-Ellis method. If the spinal meninges are more or less acutely inflamed, 1.35 mg. of neoarsphenamine in 60 cc. can be given safely twice a week according to Gennerich. If the cord is metasyphilitically changed never more than from 0.3 to 0.5 mg. should be given in from 40 to 60 cc. of spinal fluid at intervals of three weeks. If a tabetic patient does not react subjectively and clinically to 0.3 or 0.5 mg. intraspinally one can increase the neoarsphenamine medication to 0.75 and 1 mg. To relieve subacute symptoms referable to a basilar meningitis, neoarsphenamine can be given intraspinally by the cisternal route in doses of from 0.5 to 1 or 1.5 mg., or by a double puncture in the lumbar regions where the liquor in the lower buret pushes the liquor containing 0.5 to 1 mg. of neoarsphenamine in the upper buret brainward. Both administrations endeavor to keep the neoarsphenamine in the basilar cisterns and necessitate rest in bed for at least thirty-six hours with the patient in the Trendelenburg position.

The statement that the introduction of the arsphenamines has resulted in an increase in neurosyphilis is erroneous. The investigations of the German-Russian expeditions which studied syphilis in the Mongolian republic Burjato at Lake Baikal proved without doubt that neurosyphilis is just as common among people who never have been treated with European antisyphilitic measures. Statistics show that only from 8.8 to 15 per cent of syphilitic persons develop paresis, and that approximately 68.2 per cent of tabetic patients have never had antisyphilitic treatment. I consider it a scientific error not to treat primary and secondary syphilis with arsenicals, but we must keep in mind always that as much harm can be done by giving too much arsphenamine as too little. Unfortunately, most syphilitic patients are undertreated. Insufficient treatment with arsenicals is more injurious than no arsenical medication. Arsphenamine is the most stable arsenical with uniform toxicity and the greatest therapeutic effect, and is superior to neoarsphenamine. The inconvenience of its preparation and administration and the exigencies of office practice have led to the substitution of other arsenical preparations. The single dose should never exceed 0.6 Gm. and it should be given only once a week. Advanced cardiovascular disease is a contraindication to its use. Neoarsphenamine has a somewhat lower therapeutic efficiency than arsphenamine and necessitates a larger number of injections. It has a marked tonic effect, produces less gastro-intestinal reaction and is less irritative to the veins. Because of its much simpler administration, its use is more widespread, at least in office practice. I do not favor spinal drainage following intravenous arsenical injections because, if the defense mechanism of the meninges as a barrier between the blood and liquor is intact, nothing is gained by this procedure whereas if this barrier is defective, exudations from the blood into the spinal fluid are present even without spinal drainage.

Disadvantages of arsphenamine and neoarsphenamine are the anaphylactoid or nitritoid crises but preventive drugs such as atropine, epinephrine and ephedrine are able to check these unpleasant occurrences. Recently

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Girard, Gougerot and Bertillon recommended dissolving arsenical preparations in a 10 per cent aqueous solution of eosin-acid cesium, which will prevent the nitritoid crisis Silver arsphenamine is said to be from two to three times as effective a spirocheticide as arsphenamine, but clinical experience has proved that it is not superior to the other arsenicals I never have seen any beneficial effects from its use that could not be obtained in greater degree from other arsenicals The arsenical preparation of choice for cases in which intravenous medication is difficult or impossible because of extreme obesity or inaccessibility of the veins is sulpharsphenamine, which is a forerunner of neoarsphenamine and resembles it closely in its chemical composition According to Cornwall and Meyers of New York, it is two and a half times less active than neoarsphenamine therapeutically Doses of from 0 4 to 0 6 Gm are given intramuscularly at weekly intervals without constitutional reactions My clinical experience with intramuscular injections of sulpharsphenamine, especially in congenital syphilis, has been very encouraging and it can be recommended highly as an effective agent in congenital neurosyphilis Sodium acetylaminohydroxyphenylarsonate, a pentavalent arsenic preparation, has not been used Many investigators recommend it highly for prophylactic therapy and praise its effectiveness in congenital syphilis It is given orally in tablets containing 2 Gm, from two to three tablets being ingested for three days on an empty stomach I feel that prophylactic syphilitic therapy should not be employed because it may mask the disease and later on, when symptoms develop which cannot be classified under syphilitic manifestations, the physician does not know whether to advise the patient that he is suffering from syphilis or not, and does not know how to manage the situation The final result will be either a syphilophobia or late manifestations of nervous syphilis

I have had no experience with bismuth arsphenamine sulphonate, which, according to G W Raiziss, is an ideal antisyphilitic remedy as it combines spirocheticidal and defense arousing properties and lacks toxic effects It belongs to those compounds in which the arsenic group is bound to a metal Stokes, Chambers and O'Leary have reported on it favorably but have had less satisfactory results in neurosyphilis than in other forms of the disease At the Wisconsin Psychiatric Institute we have experimented for the last nine years with arsenical preparations which were chemically and biologically studied by the late A S Loevenhart

I am convinced more than ever that tryparsamide is superior to all other forms of intravenous arsenical treatment in neurosyphilis I could report a number of cases in which, in three years, from 14 1 to 17 9 Gm of neoarsphenamine with from fifty-one to sixty-six injections of mercury was given without any clinical or serologic improvement These cases have shown clinical improvement and completely negative serologic reactions after from twelve to sixteen injections of tryparsamide in combination with from thirteen to sixteen injections of mercury This may indicate that cases given preparatory treatment with arsphenamine, neoarsphenamine, bismuth or mercury will respond more favorably to subsequent tryparsamide therapy Whether tryparsamide is primarily a resistance builder as manifested by the gain in weight averaging from 2 3 to 18 Kg, or primarily a healer of lesions, as a result of spirocheticidal action, cannot be answered as yet, as sufficient pathologic reports are not available Generally the dosage of tryparsamide is 3 Gm per injection, but individual case adjustment necessitates variable doses of from 2 to 5 Gm with a considerable latitude as to the intervals during its administration W F Lorenz reported at the last meeting of this section our indications in the use of tryparsamide and the results that we obtained during the last six years I must correct the statement often referred to in reports dealing with tryparsamide that the drug carries a menace to the optic nerves Optic atrophy is not caused by arsenicals and especially not by tryparsamide, but by the disease itself If the eye studies reveal impairment of the optic tracts, one should not use arsenicals, or should employ them very cautiously The tonic effect of arsenical medications stimulates the present interstitial and perioptical inflammation and will lead to advancement of the disease, resulting in visual constriction and even optic atrophy

Severe lancinating pains and gastric or renal crises require doses of from 4 to 5 Gm of tryparsamide given at intervals of two weeks over a period of twelve weeks, or malarial therapy if optic atrophy is present As a rule we prepare our patients, especially those with tabes, with mercury inunctions and potassium iodide over a period of from four to six weeks before we decide whether they should have arsenical medication, especially tryparsamide I feel that mercury is absolutely equal in efficiency to bismuth and have not substituted bismuth for mercury for this reason I have not seen toxic effects from mercury when mercury is used in the form of inunctions or weekly intramuscular injections of from 0 05 to 0 1 Gm of the salicylate in a palmitin base In the treatment of mild tabes I follow more than ever the recommendation of Nonne, that is, mercury inunctions and potassium iodide for a period of from six to eight weeks, to be repeated every six months Oppenheim stated one year before his death that a tabetic patient without a distinct tendency to progress was better off without vigorous antisyphilitic therapy In our treatment of syphilis of the central nervous system, the iodides take an important place Each patient receives iodides previous to arsenical injections It is not advisable to use large doses From 3 to 10 minims (0 18 to 0 6 cc) three times daily is sufficient to dissolve granulomatous tissue and enhance the penetrability of arsenicals, mercury or bismuth

CONCLUSION

Finally I wish to stress the importance of individual case adjustment in central nervous system syphilis Preparatory therapy, preferably mercury inunctions and iodides for from one to two weeks, is to be recommended before the most suitable arsenical preparation is employed I favor among the arsenicals tryparsamide and, next to that, neoarsphenamine in cases without optic tract involvement, and warn against the use of any arsenical in advanced parenchymatous cases The latter should be treated by nonspecific methods, among which malaria is the most efficient Sulpharsphenamine has been the drug of choice in the treatment of congenital syphilis, but I have had good results in a number of cases of congenital neurosyphilis that have been treated with malaria followed by tryparsamide and mercury in the case of paresis, and tryparsamide combined with mercury and iodides in juvenile tabes I would advocate the same treatment for the congenital forms as for the acquired forms of neurosyphilis

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS O LEARY AND BRUNSTING AND DR. REESE

Dr. Franklin G Ebaugh, Denver Tryparsamide has proved to be one of our leading drugs in the treatment of neurosyphilis Malaria therapy followed by other methods of nonspecific therapy has also improved the generally unsatisfactory results existing a decade ago Our cases have been entirely unselected Since 1925 we have treated 171 cases of neurosyphilis, chiefly paresis Nonspecific therapy, sodoku, malaria and typhoid vaccines have been used. The malaria inoculation has proved the most effective and has been instituted as a routine procedure, combined with tryparsamide and arsphenamine and general therapy Of the 171 patients treated now available for statistical consideration, ninety-nine, or 58 per cent, have been returned to the community, forty-five, or 27 per cent, are living but unrestored, and twenty-seven, or 15 per cent, are dead At present there are sixty-four cases of postmalarial neurosyphilis under active treatment in our outpatient department These patients have been followed closely year by year by our social service department Thirty-two of the sixty-four are now working Twenty, or 31 per cent, are not able to work, four, or 6 per cent, are unable to secure work, five, or 8 per cent, are housewives, and three, or 5 per cent, are children. Using clinical criteria alone as a standard we find that approximately 23 per cent attain complete remissions, 30 per cent attain incomplete remissions, and 5 per cent attain slight improvement sufficient to avoid complete invalidism It seems to me that we can now make a definite summary of this type of therapy First, malaria therapy is at present the best known method of treating neurosyphilis, and should be combined with tryparsamide or arsphenamine. Second, complete remissions may occur in all the clinical types of neurosyphilis Third, a case that does not go into the remissive stage may show a prolonged and marked physical improvement Fourth, malaria does not seem to be as successful in the treatment of women as of men Fifth, juvenile paresis, as a rule, does not appear to be benefited by this type of treatment Sixth, a comparison between specific and nonspecific and a combination method of treatment should continue and should lead to a formulation of the definite therapy of the future. Seventh, our present diagnostic and prognostic criteria present many inaccuracies Unknown forces operate in producing or in not producing a remission, and our present-day social and economic standards as criteria of remissions appear inaccurate.

Dr. A A Herold, Shreveport, La Although I hail from Louisiana, supposed to be the hotbed of malaria, on several occasions when I wanted fresh cultures or specimens of active malarial blood, I was unable to procure them Dr Ebaugh referred to other agencies than those mentioned by Drs O Leary and Brunsting, one of which was sodoku I have seen some remarkable results from sodoku In New Orleans they keep a culture of a very active sodoku or ratbite fever with which they inoculate the paretic patients, and some of the results have been fully as good as those obtained with malaria treatment The advantage is that one dose of arsphenamine or neoarsphenamine will stop the sodoku immediately So far as arsenicals are concerned, my experience has been that we may expect more results from the tryparsamide than from any other arsenicals We have been cautious to watch the eyes in administering it, for it is supposed to have an unusually injurious effect on them, but in my experience I have never seen any bad effects on the eyes from the use of tryparsamide. I have treated several small children with congenital syphilis with this drug and I have obtained marked clinical improvement but the serologic improvement was always slow in my experience

Dr Theodore Diller, Pittsburgh In 1903 a man presented himself with a typical case of tabes paresis I saw him several times, and then he disappeared from my sight About a month ago he returned to the office after twenty six years His condition seemed to be just about as it was in 1903 He had had no treatment of any sort It was one of those cases of arrested development or arrested progression It was a consideration of such cases that made me slow to accept the improvement following malarial treatment Even now I feel that we must be cautious and go at the matter with some reserve However, these doubts were a good deal dissipated last summer when I met Professor Wagner and examined a large number of patients in his clinic. He has treated more than a thousand, I think his figure is 1 600 I saw many of these patients and studied their records and it was really remarkable to see how well they were doing It was also remarkable to see how eager these patients were to return to the clinic for reexamination.

Dr. Walter Freeman, Washington D C. The question used to be in regard to malaria Will it work? We have solved that, I think. It does work Now the question is Will it last? and the report of Dr Brunsting seems to indicate that it will last. In calculating surgical recoveries, five years is usually considered adequate May it not be the same in the case of these mental diseases? I merely wish to indicate how long such a remission may last from some of my experience in the pathologic service at St Elizabeth s Hospital Three patients came to necropsy in the stage of arrested paresis, so called, one having been admitted in 1911, another in 1913 and another in 1914 These men had completely developed paresis at the time of admission, and yet they attained a quiescent state Even the serologic changes were reversed practically to normal In going into the history of these men we found that in two cases there had been attacks of malaria shortly before or shortly after admission to the hospital, and the other man had suffered from a severe pleurisy with pneumonia and high fever The necropsy observations left me doubtful as to the syphilitic etiology of one case, but in the other two cases there were definite scarrings of the aorta and puckerings in the capsule of the liver that indicated a previous syphilitic infection. These patients died not of paresis but of a cardiac disorder, or some other condition That, it seems to me, indicates that these arrested cases might almost be termed recoveries

Dr. Walter L Bruetsch, Indianapolis Evidence is accumulating from the clinical as well as experimental side that temperature plays only a subordinate role in the mechanism of malaria therapy In 1926 a colored paretic patient was treated with malaria at the Central State Hospital of Indiana While under treatment the patient never had any rise in temperature Blood smears, however, showed the presence of plasmodia and a moderate monocytosis The patient improved physically but remained in the institution The amazing feature in this case was the serologic reaction, which improved gradually and after two and one half years was reversed to normal Furthermore, the finding of spirochetes in the brains of malaria-treated patients speaks against the assumption that temperatures which can be produced with safety in man are capable of destroying syphilitic organisms In a paretic patient who was treated twice with malaria and who has had elevations of temperature ranging between 104 and 105 F I was able to find spirochetes in the brain cortex on histologic examination If, therefore, the rise in temperature is not the main factor in bringing about the improvement one can look for an explanation on the basis of specific tissue changes The histologic changes under malaria treatment consist, broadly speaking of a stimulation of the reticulo-endothelial system, leading to new formation of phagocytic tissue in all the organs of the body The increase in weight of the liver and spleen which is found in patients who die under malaria treatment is mainly due to an almost tumor-like growth of phagocytic tissue Moreover, proliferative phenomena in the capillary endothelium of the brain and internal organs take place which are evidenced by the appearance of blood histiocytes in the veins of the internal organs This endothelial phase apparently is connected with the reduction of the increased permeability of the brain capillaries which is noted in those patients who respond well to malaria therapy It seems that these two phases of therapeutic malaria new formation of phagocytic tissue and endothelial stimulation of the cortical capillaries, are two factors which among others are responsible for the beneficent effect of malaria treatment

Dr L A Brunsting, Rochester, Minn Our experience with fever therapy has been limited to the use of inoculation malaria and typhoid vaccine intravenously Following a suitable course of fever the patient is given a rest period of about six months and the matter of further therapy is taken up after reconsideration at the end of that time Some of the paretic patients in particular may be given further courses of fever by means of typhoid vaccine, or specific measures such as tryparsamide or the Swift-Ellis intraspinal treatment in repeated courses in the usual fashion over an extended period of time There are some persons who seem to be naturally immune to the malaria, refusing it altogether or tending to abort the series after a few preliminary paroxysms In these we have had no appreciable success with reinoculation and deem it more expeditious to carry on with intravenous injections of typhoid vaccine In order to achieve a satisfactory response it is sometimes necessary to use enormous numbers of bacilli with each injection and to carry the series through for a total of about twenty good reactions In general, the best results have been obtained in those patients who have developed vigorous systemic reactions with high fever sometimes reaching 105 and 106 F There have been no serious manifestations of idiosyncrasy to quinine. Relapses of malaria have occurred in a few rare instances but these have been easily controlled by further quinine therapy There are certain types of patients in whom it would be well to postpone the use of such measures as malaria, particularly the extremely agitated paretic patient and also the patient with taboparesis showing considerable lower cord involvement and especially disturbances of the genito-urinary system. Deaths directly attributable to malaria are fewer as experience grows both in the selection of cases and in the recognition of complications such as jaundice and early uremia during the course of malaria

Dr. Hans H Reese, Madison, Wis I have treated patients since 1900, and a great number were restored practically to normal health and have returned to their former occupations In that first group from 1927, about eighteen cases are still in complete remission or are clinically arrested

CHEST ROENTGENOGRAMS OF NONTUBERCULOUS CHILDREN SUSPECTED OF BEING TUBERCULOUS *

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AND

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There exists a marked confusion in the interpretation of the shadows in the roentgenograms of children's chests This is well illustrated by the recent paper of Hawes and Friedman [1] in which it was shown that no agreement existed in the six separate interpretations of a series of films given by a pediatrician, two tuberculosis specialists and three roentgenologists The basic reason seems to be that there is no general agreement on the possible changes to be seen in a nontuberculous chest This preliminary study was undertaken to determine the condition in the chests of nontuberculous children in order to establish a basis for a further study of the chests of tuberculous children

The cases studied were referred to the Children's Chest Clinic of the University of California Hospital because they represented symptoms suggesting tuberculosis or were regarded as possible contact cases The control group consisted of normal children from the Institute of Child Study, University of California, Berkeley A complete clinical history was taken and a physical examination was made of each patient All of them were tested with human tuberculin in the concentration of 1 1,000 and 1 100 and with a broth control, by the intracutaneous injection of 0 1 cc The reactions were observed after forty-eight hours The group selected for study consists of those who did not react at all to the tuberculin It is assumed that, when obtained in the absence of any acute condition, the negative tuberculin reaction indicates that no infection with the tubercle bacillus exists or has previously existed This is generally accepted at the present time

The roentgenograms were made with a routine technic For the younger children the distance was 42 inches (106 7 cm) with the child prone, and for the older children, 48 inches (122 cm) with the child upright in the postero-anterior position The x-ray tube was centered on the fifth dorsal vertebra Lateral films were made in most cases The films were made during a period of four years and the time of exposure decreased as better equipment became available, to the present exposure of one-tenth second The general character of the films obtained is such as can be reproduced in all well conducted x-ray departments We are well aware that with special methods, such as the synchronized roentgen exposures used by McPhedran or the constant exposure time of Wasson, greater accuracy is possible, but their observations cannot often be duplicated at present by the general clinic The present study is justified because the results can be utilized generally

The roentgenograms present shadows of densities and localizations that have to be interpreted in terms of normal and abnormal morphology McPhedran,[2] Armand-Delille,[3] Sterlin and Chaoul,[4] Engel [5] and others attempted to correlate the observations in roentgenograms made before and after death with pathologic examinations conducted particularly for this purpose The results of their studies make the following interpretations seem reasonable

The hilar shadow is cast by the main stem arteries, veins and bronchi Paratracheal and all bronchial lymph glands, unless calcified, show only when they are so enlarged as to extend beyond the shadows of the main stem McPhedran concludes that "calcium-free glands, however enlarged, fail to cause perceptible intensification of the mediastinal shadow" The hazy perihilar shadows frequently seen are not due to enlarged bronchial glands or fibrosis but to pulsation and resultant vibration of the arteries McPhedran has clearly shown that this vibration is not eliminated by exposures even of one-fortieth second unless they are made in late diastole

Calcification of the glands is recognized by a shadow of granular appearance The shadows frequently interpreted as calcification are due in reality to vessels running axially to the x-rays These are homogeneous in density and round or oval Their density depends on the distance they run axially and may be as great as or greater than that of a calcified gland This can be proved by making a second exposure of equal density from a different angle It may be necessary

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* From the Department of Pediatrics the Department of Roentgenology and the George Williams Hooper Foundation for Medical Research University of California Medical School and the Institute of Child Welfare University of California.

[1] *Hawes* J B 2d, and Friedman Eli Interpretation of Roentgenogram in Tracheobronchial Gland Tuberculosis J A M A **92** 609 (Feb 23) 1929

[2] *McPhedran* F M *Am* J M Sc. **173** 313 (March) 1927

[3] Armand Delille, P F and Lestocquoy C. Tubercle **9**: 359 (May) 1928

[4] Stierlin E and Chaoul H in Sauerbruch Chirurgie der Brustorgane Berlin *Julius Springer 1925*

[5] Engel S Ergebn. d inn Med. u Kinderh **11** 219, 1913

to make a shift greater than the routine stereoscopic so that the vessel no longer runs axially to the ray In this film the shadow can no longer be seen

The normal markings seen beyond the hili are due to a combination of bronchi and vessels, the vessels assuming a more important rôle as the periphery is approached The interpretation of increases in these markings is still in doubt It is definitely known that vascular congestion produces increased shadows Whether other increases in the markings are due to fibrosis of the peribronchial tissue or to decreased elasticity of the lung, and hence to lessened vibration, is still uncertain In the present study, localized increases in the markings are recorded without reference to the definite explanation of such increases

Roentgen and Clinical Observations on the Chests of Nontuberculous Children

	Children's Chest Clinic	Institute of Child Study	Hilus: Multiple Large Vessels Both Hili	Hilus: Single Large Vessel in Either Hilus	Lung: Multiple Axial Vessels Up to 2 Mm Upper Left Lobe	Lung: Multiple Axial Vessels Up to 3 Mm Upper Left and Right Lobes	Lung: Increased Markings in Either or Both Upper Lobes	Without Increased Markings	Interlobar Pleura Thickened Interlobar
Total number in									
Children's Chest Clinic	93		74	24	40	19	35	58	12
Institute of Child Study		20	18		11	0	3	17	2
Percentages									
Children's Chest Clinic			70	26	43	20	37	62	13
Institute of Child Study			90		55	0	15	85	10
Average per child									
Respiratory diseases	2.3	1.7	2.4	2.4	2.5	2.6	2.2	2.4	2.1
Symptoms	1.4	0.8	1.4	1.8	1.6	1.4	1.5	1.4	1.8
Age	8.0	3.5	8.2	9.3	7.9	0.9	7.9		7.5
Contact, per cent	38	5	39	42	37	27	43	34	75
Noncontact per cent	62	95	61	58	63	63	57	65	25
Previous diseases (percentages)									
Bronchitis	46	40	47	42	55	37	40	50	58
Pertussis	45	20	45	58	53	47	51	41	17
Measles	57	15	61	62	55	42	46	64	50
Pneumonia	19	5	10	16	20	16	17	21	16
Disease of the upper respiratory tract	60	90	59	58	65	63	63	58	70
Asthma	3	0	4	4	2	5	0	5	0
Symptoms (percentages)									
Loss of weight	17	15	16	25	18	32	17	17	25
Poor appetite	23	15	26	21	30	16	23	24	8
Listlessness	18	25	19	33	23	5	23	15	32
Nervousness	31	25	26	42	38	26	31	33	56
Cough	31		26	28	30	42	37	28	33
Night sweats	15		15	21	15	10	14	15	8
Sleep disturbed	9		11	4	8	21	3	12	17
Signs (percentages)									
D'Espine's below the fourth thoracic vertebra	44	5	85	64	54	30	42	40	55
Vertebral dulness	9		7	14	21	17	12	7	18
Paravertebral dulness	23	5	18	10	17	24	25	17	63
Manubrium sterni dulness	30	10	26	18	26	32	39	22	45
Pathologic percussion	6	0	6	22	8	5	11	3	8
Pathologic auscultation	34	15	45	42	38	42	37	33	42
Limited expansion	3		4	8	2	5	3	3	0
Cervical glands enlarged	72	45	51	79	65	74	77	68	64
Tonsils enlarged	37	15	29	37	25	32	29	43	32
Tonsils removed	26	30	23	16	40	47	23	28	25
Normal weight	44	90	29	38	42	47	51	40	59
Malnutrition	40	10	30	46	45	26.5	40	40	41
Overweight	17		15	16	13	26.5	9	22	0
Clinical diagnosis									
Chest normal	42		45	38	38	53	34	46	25
Bronchitis acute	4		6	0	7.5	5	3	5	0
Bronchitis subacute	11		7	8	15	16	14	9	8
Bronchitis chronic	3		4	4	7.5	5	3	3	8
Enlarged bronchial glands	35		31	38	30	16	40	32	51
Asthma	3		4	4	2	5	0	5	0
Healed pneumonia	2		3	8	0	0	6	0	8

Axial vessels are frequently seen throughout the lung shadow but are nearly always in direct relation to other vessel markings

The method adopted for this study was to tabulate for each case a complete clinical summary and all definite data from the x-ray films and attempt to see whether there was any correlation between the two On the clinical sheet were listed the age, contact or noncontact, previous diseases (bronchitis, pertussis, measles pneumonia, repeated upper respiratory diseases and asthma), symptoms (loss of weight, poor appetite, listlessness, nervousness, cough, night sweats and disturbed sleep), physical signs (d Espine s sign, vertebral dulness, paravertebral dulness, dulness of the manubrium sterni, abnormal observations on percussion and auscultation and any limitation of expansion), nutrition, any enlargement of the cervical glands, condition of the tonsils and the diagnosis

From the x-ray films were listed the following data for each hilus separately, the size, position and consistency of any shadow of calcification, the presence or absence of any glandular tumor, the number, size and position of all axial vessels, and any localized increase in the density of the hilar shadow, for each lung, the size, position and consistency of any shadow of calcification or infiltration, the density, width and localization of increased lung markings, the size, position and number of any axial vessel markings and nodular shadows, and for the pleura, any localized increases in density

The following observations on the ninety-three cases were compared with those for twenty normal children examined at the Institute of Child Study in Berkeley

No calcifications were found in either the hili or the lung fields, with the doubtful exception of one small, slightly granular shadow in the lung tissue

No glandular tumor was found

There were seventy-four cases in this series with multiple large axial vessels in the hilus on both sides, and twenty-four with a single large axial vessel on each side

No localized increases in the density of the hilar shadows were found

No localized shadows were seen in the lung that could be interpretated as areas of infiltration

There were thirty-five cases in which localized increases in the width or density of the lung markings were seen in either upper lobe The sharp, clear-cut bronchial tree markings seen in tuberculosis of adults were not found in a single case The increase was just sufficient to mark those mentioned from the others present or normally expected No studding of these markings was noted

Forty cases were found in which there were multiple axial vessels up to 2 mm in diameter in the upper left lung field, there were many more in the upper right lung field There were nineteen cases with multiple axial vessels up to 3 mm in diameter in each upper lung field

The only area of increased pleural shadow in more than two cases was the interlobar fissure between the right middle and upper lobes, this observation was made in twelve cases

The clinical data on all the cases showing each of the roentgen characteristics described were listed in separate groups, and the percentages of each previous symptom, sign and diagnosis were calculated Finally, all groups were united into one table

Taking a few facts from this table, it is seen that

1 The average number of previous diseases per case varied only from 2 2 to 2 6 for the various groups, with the whole series at 2 3

2 The average number of symptoms presented by each group varied between 1 4 and 1 8 per case

3 The average age of the whole series was 8 years, the youngest patient being 2 years of age and the oldest 15

4 Of especial interest is the observation that the group without increased markings in the upper lobes had a higher incidence of past respiratory diseases, especially bronchitis, measles and pneumonia, than the group with increased markings

5 The Institute of Child Study group with an incidence of previous disease of 1 7 per child and with an average age of 3 5 years showed in comparison with the clinic group a higher percentage of multiple axial vessels at the hili, a slightly higher percentage of multiple axial vessels up to 2 mm in diameter in the upper left part of the chest, no vessels of 3 mm in either lung field, and a somewhat lower percentage of localized increases in the lung markings

6 There was no increase in the number showing positive d'Espine's sign, vertebral dulness, paravertebral dulness and dulness of the manubrium sterni in the cases presenting multiple axial vessels at the hili

The definite impression gained by a survey of the whole table is that there is no marked variation in any of the groups One exception to this observation is the group of twelve cases showing the interlobar pleura, which is obviously too small a group to consider

CONCLUSIONS

1 The roentgenograms of the chest of children without acute illness and giving a negative tuberculin reaction may show single or multiple, large or small axial vessels in the hili, multiple axial vessels up to 2 or 3 mm in diameter in the lung tissue, localized increased lung markings, localized pleural thickenings, or none of these shadows It is therefore apparent that a diagnosis of tuberculosis of the mediastinal glands or lung tissue cannot be based on these observations

2 No calcifications, glandular tumors or localized pulmonary infiltrations were found

3 No definite correlation was found to exist between the positive roentgen observations and the clinical history

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ABSTRACT OF DISCUSSION

Dr Frank C Neff, Kansas City, Mo There is need for a standard or basis for determining what a roentgenogram of the hilus really means in children We must know more about two things in our interpretation of these roentgenograms The first is to determine whether we can tell the difference between these small areas which are sometimes interpreted as small glands and which Dr Wolff shows are really the shadow caused by the blood vessel which runs at right angles to the film He says that it is not entirely a matter of the size of these which determines it but that a shadow which represents a deposit of lime in the tissues really presents a granular appearance The other question is this If we are going to come to any conclusion about the interpretations of films, we should consider the value or the relationship of the tuberculin skin test to these conclusions I was rather surprised to find that Krause is quoted as saying that tuberculosis, particularly of the glandular type, may so entirely disappear that even the skin reaction will become negative. Some no doubt read the communication in the *American Review of Tuberculosis* a couple of years ago by Bitter and Meyers in which they stated that nearly as many children with calcified hilus glandular tuberculosis show negative skin tests as positive skin tests Those two things are rather disquieting if one tries to come to any conclusions from a correlation of the films with the symptoms

Dr F M Pottenger, Monrovia, Calif To differentiate between a tuberculous and a nontuberculous lesion of the lung by roentgenograms often requires great skill and much experience in interpretation The tuberculin test, if positive, is valuable because it shows that a tuberculous infection is present, but it does not indicate that the lung lesion is clinically tuberculous Dr Neff's question of how long sensitization will last after a lesion is healed is interesting and important. Krause followed a case through active tuberculosis to complete healing and final disappearance of sensitization As I remember it, he followed his patient four or five years after healing I think we can assume that sensitization will disappear after a time when caused by small lesions which completely heal I have tested, fifteen or twenty years after treatment patients who had previously suffered from advanced lesions, and found that sensitization was gone in some of them The roentgenogram does not show everything It will show calcification, unless the calcification happens to be low in the lung, so that the shadow is immerged into the liver shadow, or behind the heart where the shadow is lost in the general shadow of that organ We know, too, that it will not always show, even if calcified and in the open lung field, because at times even the scapulae are not visible in a roentgenogram, and they contain more calcium than some small tuberculous lesions Our minds are too much set on a calcified node of some size in the primary lesion Doubtless many primary lesions are no more than a small scar, others, a calcified node no larger than a pinhead, the main part of the primary complex being the lesion in the lymphatic nodes Unless the calcified nodule is in the proper plane, it may fail to cast a shadow on the plate Those which lie in the plane nearest the plate will show most readily, while those that lie nearest the tube may totally fail to intercept the rays sufficiently to cast a shadow Primary nodules which have healed by fibrosis may fail entirely to cast an interpretable shadow A plate taken at 5 feet, or 2 meters, will show lesions that fail to appear on the plate when taken at 3 feet Groedel has suggested that the plate may still be improved by having the patient stand 20 cm from the plate. Tuberculous lesions that are not calcified may not show any shadow The authors emphasize rightly the importance of shadows that are caused by blood vessels, which make for certainty in diagnosis

Dr Ernst Wolff, San Francisco A negative tuberculin test may be obtained in one who was never infected or in a patient in whom tuberculosis is healed All of the latter cases, which are rarely found, were cases without clinical symptoms Dr Neff's case probably belongs in this group Of the 600 children who were followed up in our chest clinic no patient with definite contact, definite exposure clinical signs and symptoms, and glandular tumors in the roentgenogram could be observed who reacted negatively to tuberculin On the other hand among our ninety-three patients who reacted negatively, no glandular tumor was observed It may be concluded that in the presence of symptoms and signs provided overwhelming infection is not present a negative test excludes tuberculosis Ordinarily the casual infection with tuberculosis does not lead to the disappearance of the specific allergy as proved by the positive skin test in nearly every healthy adult When we have to answer the parents' question Is our child tuberculous?' we can rely on a negative reaction provided the test is done with properly prepared tuberculin and with good technic.

FRACTURES OF THE BONES OF THE FOOT OTHER THAN THE OS CALCIS*

W L BROWN MD
AND
C P BROWN MD
EL PASO, TEXAS

According to Bacon,[1] "in the total expense for loss of time, fractures of the metacarpals, metatarsals and phalanges of both extremities exceed those of all other fractures combined, excluding awards for permanent total disability "

While this undoubtedly is true and while fractures of the bones of the feet are most frequent of all, they are most often undiagnosed We think that this may be partially due to the fact that we have always been taught that fractures of the bones of the feet were easily diagnosed Proceeding on that theory, we have allowed at least a third of them to pass for from two to four weeks, if by that time the patient had not recovered, we have had roentgenograms made By then, however, the harm had been done and the diagnosis, except as to its effect on the prognosis, was of but little value

ETIOLOGY

The next most important factor is the lack of realization as to the ease with which a fracture of the small bones of the foot may occur It is hard for many to understand that the mere turning of the foot while walking or dancing, stubbing of the toe or the dropping of a small weight on the foot may cause fractures which, if not recognized, greatly prolong the disability

While these fractures are most likely to be in the phalanges or fifth metatarsal, the second metatarsal has been known to be fractured by the dropping of a piece of two by four, weighing 2 pounds 10 ounces a distance of 8 feet Therefore if we will constantly keep in mind that the simplest trauma will cause a fracture, we shall examine roentgenographically at least 25 per cent more of these trivial injuries and thereby save ourselves much chagrin and the patient much suffering and disability

DIAGNOSIS

The stereotyped statement that the diagnosis is easily made because the bones are superficial must be disregarded, if we expect to improve on our diagnosis and treatment of the fractures of the foot It is especially important that the diagnosis be made immediately when fractures involve the bones on the inner or weight-bearing side of the foot, which compose the longitudinal arch When the diagnosis is not made in these cases there may be, in addition to prolonged morbidity, more or less permanent disability

DIVISIONS

In treating fractures of the bones of the foot other than the os calcis, we prefer to visualize the anatomic divisions of the foot in relation to their importance to function following fracture We therefore have adopted the following grouping

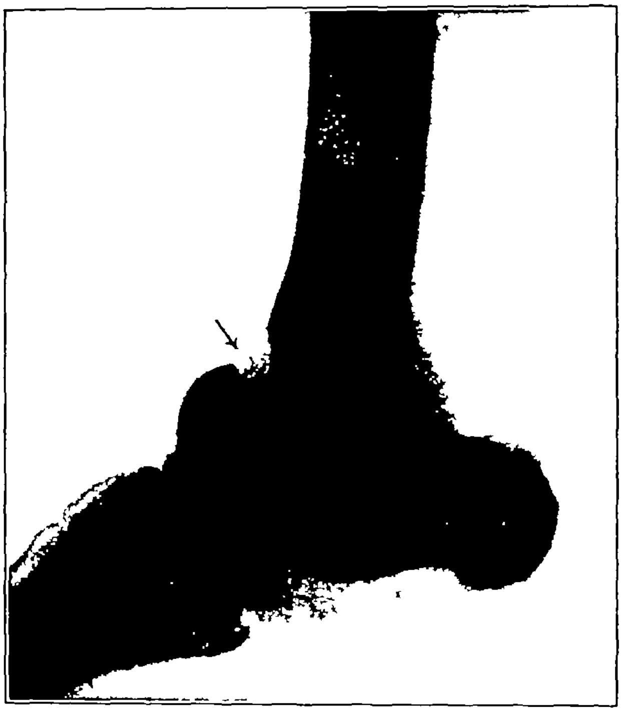

Fig 1 —Fracture dislocation through the neck of the astragalus. In this case it was necessary to remove part of the free fragment before reduction could be accomplished

1 Astragalus
2 Inner tarsals, which with the first, second and third metatarsals constitute part of the longitudinal arch
3 The fourth metatarsal
4 The fifth metatarsal
5 Phalanges and sesamoids

Astragalus —These fractures are probably the most serious of all in their consequences they are usually caused by falling and lighting on the foot stiff-legged, they may be caused by extreme dorsal flexion or during other severe traumas to the foot, they are often called sprain ankles

Frequently there is no displacement In such cases, if the fracture is recognized and the foot dressed in extreme flexion in molded plaster there is likely to be slight, if any, permanent disability Fractures or fracture dislocations of the body are much more serious and are caused by much more serious injuries to the surrounding parts

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* Read before the Section on Orthopedic Surgery at the Eightieth Annual Session of the American Medical Association Portland Ore. July 11 1929

[1] Bacon J D A Review of 3 473 Fractures Southwestern Med. June 1929

In these cases, after careful roentgen studies, the patient should be anesthetized, and with the foot flexed at a right angle and the lower leg flexed at a right angle, the achilles tendon is relaxed and the fragments are molded into place

If all efforts to obtain reasonably good reduction fail, there should be open operation with removal of one or all of the fragments, if necessary This is always a serious procedure and if there is a surgeon near by who is well trained in such treatment, the patient should be transferred to him

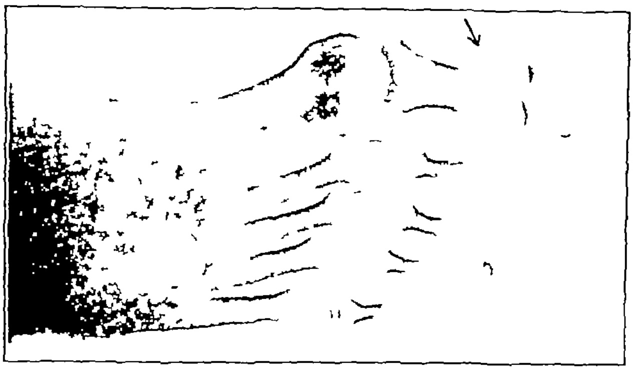

Fig 2 —Fracture of the first phalanx of the great toe involving the joint. The condition remained undiagnosed until a roentgenogram was taken

The earning capacity for laborers is reduced from 25 to 30 per cent except in the simple fractures of the neck With this bad prognosis these cases should be placed in the hands of an expert at the earliest possible moment

Gray[2] estimates the average cost to industries for these injuries at $944 This certainly is a very low figure

Inner Tarsals—These bones with the first, second and third metatarsals forming the anterior part of the longitudinal arch make fractures of the inner part of the foot second in seriousness only to those of the astragalus This group, with the os calcis and astragalus forming the weight-bearing part of the foot and giving the foot its elasticity, makes fractures of any of its component parts very important in their relation to the future function of the foot The anterior pillar of the longitudinal arch is composed of the heads of the first, second and third metatarsal bones and the posterior pillar of the os calcis

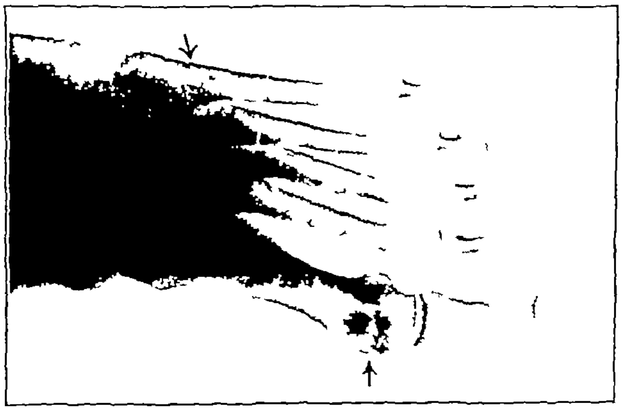

Fig. 3 —Fractures of the outer sesamoid of the great toe and of the neck of the fifth metatarsal from turning the foot while walking

Fractures of the tarsal bones are quite infrequent except when associated with extensive fractures of the whole foot However, fractures of the metatarsals are frequent, and the diagnosis depends on general points of diagnosis for fractures

Fractures of the first, second and third metatarsals often have considerable displacement on either the dorsal or the plantar surface

When these fractures are overlooked there is likely to be depression of the longitudinal arch, painful pressure points and false weight-bearing lines with chronic foot ankle, knee, thigh and pelvic strains

The patient should be anesthetized and with traction on the front of the foot and counteraction at the ankle, the fracture should be molded into place as accurately as possible It should be dressed with a plaster splint molded high up under the arch and reaching to just below the knee

The special splint of Dr George G Davis[3] would appear to be of great value and is well worth referring to

Fourth Metatarsal—The diagnosis and the treatment of fractures of the fourth metatarsal are the same as in those of the first, second and third metatarsals While the fourth metatarsal does not enter seriously into the longitudinal arch, any material displacement on either the dorsal or the plantar surface would cause disagreeable points of pressure and foot disability

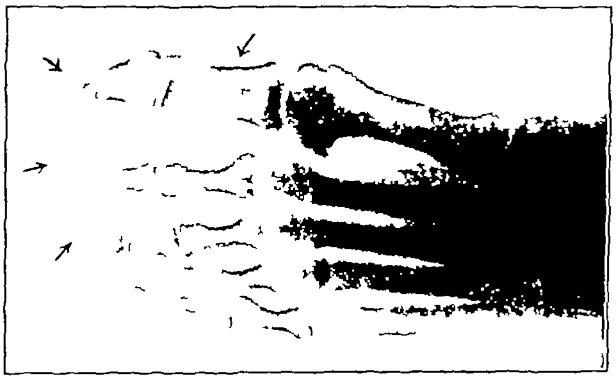

Fig 4 —Multiple fractures of the phalanges Three of these fractures were unrecognized until a roentgenogram was made

Fifth Metatarsal—Because of its location and the attachment of its ligaments and tendons this bone has a peculiar group of fractures quite independent of all the others It is the one metatarsal in which the sprain and traction fractures occur

Carp[4] states that 'the exposed position of this bone is a predisposing factor for its injury by direct violence, such as a blow, a fall, striking the outer side of the foot against a hard immovable object, and by the wheel of a vehicle in motion The indirect violence is usually a forcible inversion of the foot accompanied by weight bearing, through a fall, a jump, a sudden step on uneven ground or dancing "

Many articles have been written on fractures of this bone The fracture occurs so easily that it is often overlooked, causing long disability and often nonunion When soreness and localized tenderness occur about its head it should be kept under constant suspicion regard-to form a good, solid union That usually takes from three to four weeks Before the plaster is removed the patient should be allowed to be up and to bear weight on the plaster, and after the removal of the plaster, straight last shoes should be applied, instead of the bedroom slipper that most of them are allowed to wear Again, there should be in this shoe a proper felt insole which supports the longitudinal arch, as well as the anterior arch

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[2] Gray R. N Disability and Cost of Industrial Fractures J Bone & Joint Surg 10 27 39 (Jan.) 1928

[3] Described by Ellis J D and Coulter J S The Management of Tarsal and Metatarsal Fractures J A M A 91 81 (July 14) 1928

[4] Carp L Fracture of Fifth Metatarsal Bone with Special Reference to Delayed Union Ann Surg 86 308 320 (Aug) 1927

Dr Walter G Stern, Cleveland I cannot quite agree with the authors as to the ease with which they diagnose fractures of the foot by means of the x-rays I believe it will be within the province of the orthopedic surgeon in talking about and teaching fracture treatment to go back to some of the old and well tested methods of the past When one of the famous painters of his time was asked how he got the wonderful results he did, what substance he mixed his colors with, he said, With brains " Thus all fractures, and not those of the foot alone, must be diagnosed not with x-rays but with brains' As we all know, x rays are not infallible and roentgenograms of the metatarsus are absolutely not infallible I have collected a series of twelve primary roentgenograms which were negative for fractures Yet roentgenograms taken from three to four weeks later plainly showed fractures of the metatarsals It seems to me that there may be something peculiar about certain fractures of the metatarsus, so that they occasionally may not show early changes in the roentgenogram How shall we tell our students and fellow practitioners to make diagnoses of fractures of the foot or elsewhere By the three points that I called attention to more than fifteen years ago of which the first is localized sharp pain located over the bone, which I call pencil tenderness, because if one applies the rubber end of a lead pencil to it it will best demonstrate the area The second point is local swelling confined more or less to the tender area, and finally local, bloody discoloration in the same area These three points are not caused by anything else So one can make a diagnosis of fracture many times in the face of poor roentgenograms or none at all on the basis of these clinical observations I did not hear discussed in the paper the complications of fractures of the foot There are some very serious complications in minor fractures of the foot, namely, disturbances of the circulation to which American surgeons and physicians pay altogether too little attention they are known to the Germans by the euphonious name metatraumatic vasomotor angiotrophoneurosis which I shortened a number of years ago to the more common angiotrophosis This condition is very common There is residual swelling discoloration cyanosis and clammy sweating of the foot in a large proportion of the cases There are also such complications as contractures and hammer toes following minor fractures

Dr Thomas A Stoddard San Francisco I should like to suggest one thing that I have found of great use in the after-treatment of these cases when the fixation apparatus has been removed. I use what I call a foot glove two pieces of leather sheeting around the foot, inside of which one puts felt for the sake of supporting the anterior arch This can be modified depending on the swelling and can be worn in any sort of slipper

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Pain and Abdominal Disease—In 90 per cent of all disease pain is a prominent symptom at some point in its course Pain is by far the most prominent symptom in all abdominal disease It is the thing most dreaded by the patient and the thing more than any other that will cause him to seek medical aid Its intensity location, radiation persistency and relation to other symptoms will often alone point to a correct diagnosis The cessation of pain in abdominal disease is always welcomed by the patient but instead of being a favorable omen, it often indicates a grave prognosis Pain is the most valuable sign to the abdominal surgeon and given but one symptom upon which to make a diagnosis he would invariably select pain. Pain in the abdomen does not always mean abdominal disease but on the other hand abdominal disease almost invariably means pain In fact, a diagnosis of any acute abdominal condition with no pain is always to be regarded with suspicion—Wallingford W H Acute Abdominal Pain *Virginia M Monthly* December, 1929

COMPRESSION TECHNIC IN GASTRODUODENAL ROENTGEN DIAGNOSIS*

P G BOMAN, M D

DULUTH, MINN

It has aptly been said that the greatest obstacle to accurate diagnosis of intra-abdominal conditions is the abdominal wall That efforts are being made to overcome this obstacle is evident when one sees the proctologist with his 32-centimeter sigmoidoscope exploring the lower region of the intestinal tract and the gastroscopist searching for pathologic conditions within the stomach If the ambitions of these specialists could be realized, there would be no need for this presentation However, between the domain of the proctologist and that of the gastric endoscopist there lies a considerable area, largely unmapped and uncharted Roentgenology has stepped in to bridge the gap left by the endoscopist That it has been successful to a large degree is evident from the role which gastro-intestinal roentgenology holds today Few physicians or surgeons would willingly practice their profession without this most valuable diagnostic aid This year marks the twenty-fifth anniversary of the beginning of modern gastro-intestinal roentgen examination, and it is fitting that brief mention be made of some of the men who have contributed to our present knowledge

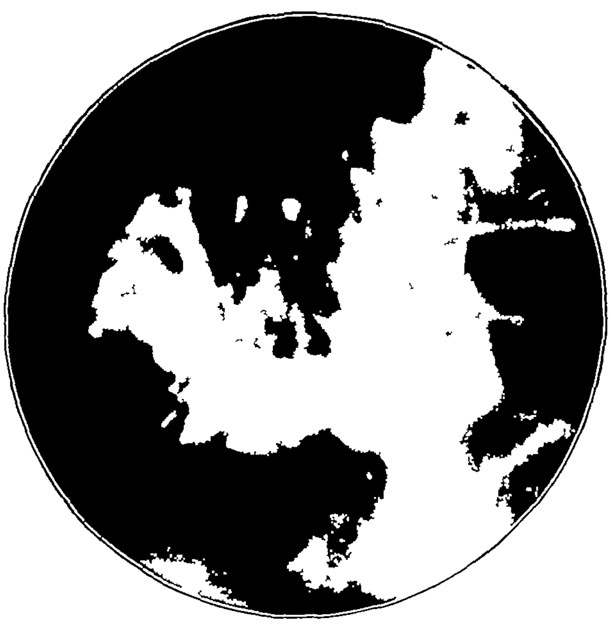

Fig 1—Normal duodenal cap with partial compression By increasing the compression the mucosal folds can be more definitely demonstrated.

In 1904, Rieder[1] introduced large quantities of bismuth subnitrate into the human stomach as a means of studying the gastro-intestinal tract roentgenographically Not only did he revolutionize gastro-intestinal roentgen examination but he foretold many great possibilities for roentgen study of the gastro-intestinal tract by this method Other men were quick to realize the advantages of this method of examination, and many contributions followed

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* From the Department of Medicine the Duluth Clinic.

* Read before the Section on Gastro-Enterology and Proctology at the Eightieth Annual Session of the American Medical Association Portland Ore July 12 1929

[1] Rieder H Radiologische Untersuchungen des Magens und Darmes beim lebenden Menchen München med. Wchnschr 51 1548 1551 1904

Reiche[2] in 1909, established certain important diagnostic principles in the diagnosis of gastric ulcer He proved from his roentgen and necropsy studies that (1) a pouchlike projection on the lesser curvature of the stomach was diagnostic of gastric ulcer, (2) a gastric ulcer would cause a disturbance in gastric motility resulting in delayed emptying of the stomach, and (3) the actual size of the ulcer did not correspond to the apparent size on the roentgenogram

Haudek,[3] in 1910, popularized the roentgen diagnosis of gastric ulcer by his careful roentgen studies and verification of his diagnosis by the surgeon or pathologist In the same year he corroborated Reiche's finding of a marked disturbance of gastric motility in cases of ulcer not involving the pylorus Two years later Haudek[4] established two important points in the diagnosis of duodenal ulcer (1) the presence of the niche as a specific sign of ulcer, and (2) distortion of the duodenal bulb either by spasm or by contracture He also observed many of the indirect signs which are of lesser importance

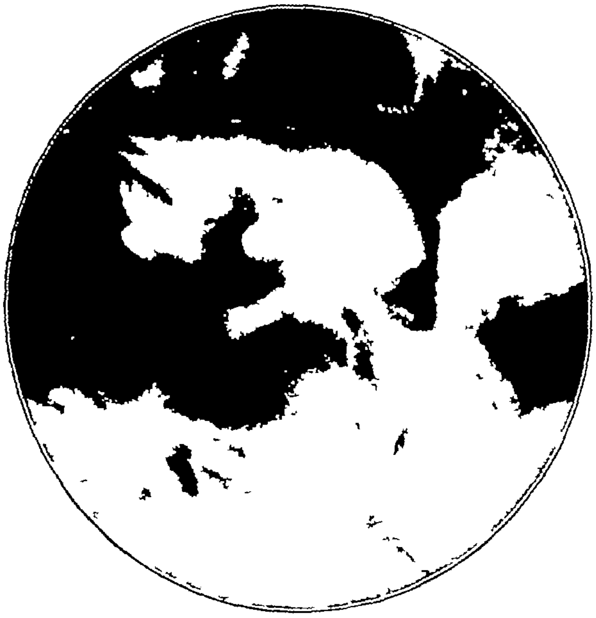

Fig 2—Duodenal ulcer on the posterior wall of the cap Without compression the bulb filled completely and assumed practically a normal outline

Baron and Barsony[5] observed a spastic hour-glass stomach in cases of duodenal ulcer and without evidence of organic disease in the stomach itself

During this time Cole[6] was studying serial roentgenograms and showing that a persistent defect in the duodenal bulb and in the stomach outline, in a series of roentgenograms, was diagnostic of organic disease

Forssell[7] made a distinct advance by his roentgen studies of the gastric mucosa This method has been further elaborated by others, including Rendich[8] and Case,[9] in the study of normal and pathologic states

Carman[10] emphasized the importance of manual compression in the visualization of pathologic conditions situated on the anterior or posterior walls of the stomach or cap

Åkerlund[11] has made valuable contributions (1) by his careful studies and analysis of the evidence in duodenal ulcer and (2) the use of compression in gastroduodenal studies

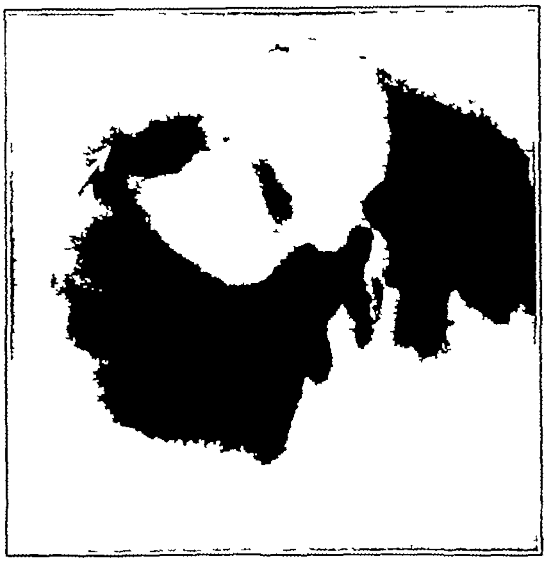

Fig 3—Duodenal ulcer on the posterior wall with compression taken in the right anterior oblique position Note the apparent swelling of the mucosa surrounding the crater

The latter phase has also been developed to a high degree by Berg[12]

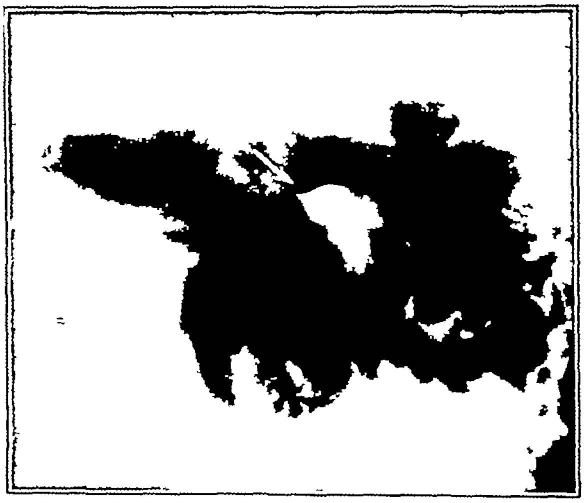

Fig 4—Penetrating ulcer on the lesser curvature of the stomach near the angularis. The size of the creater and the surrounding changes can be demonstrated much more clearly than by complete filling without compression

Many others have added valuable information and have contributed to the present status of our knowledge

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[2] Reiche F Zur Diagnose des Ulcus ventriculi im Röntgenbild Fortschr a d Geb d Rontgenstrahlen **14** 171 173 1909

[3] Haudek M Zur rontgenologischen Diagnose der Ulzerationen in Pars media des Magens Munchen med. Wchnschr **57** 1587 1591 1910.

[4] Haudek M Personal communication to the author

[5] Baron A and Barsony T Spastischer Sanduhrmagen bei duodenalen Affektionen Wien klin. Wchnschr **25** 1185 1187 1912

[6] Cole L G The Diagnosis of Postpyloric Ulcer by Means of Serial Radiography Lancet **1** 1239-1244 1914

[7] Forssell G Personal communication to the author

[8] Rendich R A. Roentgenographic Study of Mucosa in Normal and Pathologic States Am J Roentgenol **10** 526-537 (July) 1923

[9] Case J T Gastric and Duodenal Roentgen Ray Findings After Operation J A M A. **85** 1385 1389 (Oct. 31) 1925

[10] Carman R D and Sutherland C G The Duodenal Niche, Am J Roentgenol **16** 101 106 (Aug) 1926

[11] Åkerlund, Å. Die Rontgendiagnostik des Ulcus duodeni mit Hinsicht auf die lokalen direkten Rontgensymptome Mitt. a. d. Grenzgeb. d. Med u. Chir **36** 577 590 1923 Later Experiences Concerning the Niche Diagnosis in Cases of Duodenal Ulcer Acta radiol **8** 538-545 1927

[12] Berg H H Personal communication to the author

In this country there appear to be among gastrointestinal roentgenologists three distinct groups. The first depends entirely on serial roentgenography, while the second maintains that roentgenoscopy is the most accurate means of diagnosis. The third group combines the two methods.

Incomplete filling and visualization of the gastric and duodenal mucosa is used by comparatively few men, and the compression technic, so highly developed by Åkerlund in Stockholm and Berg in Berlin, is comparatively unknown in this country. Stimulated by the high degree of accuracy in gastroduodenal diagnosis evidenced in the clinics of Åkerlund and of Berg, I have introduced their method, with some modifications, in our routine gastroduodenal roentgen examinations. After almost a year's experience with this method we are firmly convinced that it has distinct merit.

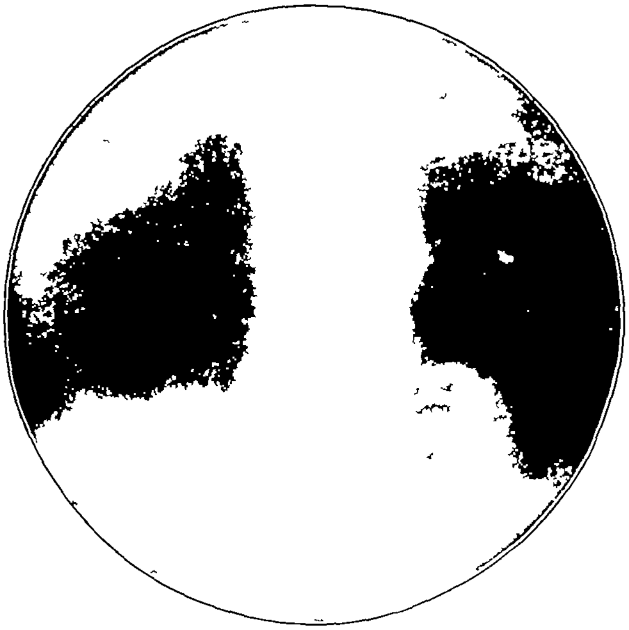


Fig. 5.—Ulcer near the middle of the greater curvature. Note the apparent depth of the crater due to the swelling of the mucous membrane surrounding it.

Comparison of the results obtained by complete filling without compression with those of partial filling with compression indicates that the latter method has much to recommend it. The results obtained in ulcer of the duodenum, pylorus, lesser and greater curvatures of the stomach, as well as the anterior and posterior walls, have been especially gratifying (fig. 1-5); likewise, the demonstration of diverticula in the stomach or duodenum has been facilitated (fig. 6). In postoperative cases, in which gastro-enterostomies or partial resections have been made, it brings out details that cannot be obtained by any other method (fig. 7).

While this method is especially applicable in the demonstration of early lesions, it also gives a clearer picture of more advanced cases. It is true that the well trained roentgenoscopist, by a combination of the direct and the indirect methods, can attain a high degree of accuracy in gastroduodenal diagnosis, but even for him the actual demonstration of direct evidence of pathologic conditions is frequently difficult. If presumptive evidence of disease can be replaced by direct evidence, there will be greater confidence in the results obtained. It is known that fluoroscopy of the chest will demonstrate a high percentage of pathologic changes, but who would discard the more concrete evidence of the roentgenogram?

TECHNICAL PROCEDURE

The apparatus used consists of a motor driven fluoroscopic and roentgenographic unit. This contains a tube suitable for fluoroscopy and roentgenography. Immediate change from fluoroscopic to roentgenographic study is accomplished by depression of a pedal at the side of the unit. The combined compression device and serialograph is suspended by counterweights and is quickly attached to the tube carrier whenever indicated.

The usual procedure consists in giving the patient from 1 to 2 ounces of barium mixture and visualizing the stomach and duodenum under the fluoroscopic screen. Manual palpation and compression as well as changing the position of the patient, are used to visualize as far as possible, the gastric and duodenal mucosa. Roentgenography can be accomplished in any position with the greatest rapidity and ease.

For more careful study of suspected areas the compression serialograph is attached and the desired compression obtained under direct fluoroscopic vision, by means of the small movable fluoroscopic screen.

When the desired compression has been obtained the casette and the screen are quickly moved and the exposure is made. By shifting the fluoroscopic screen and turning the casette, four exposures are obtained on an 8 by 10 film (fig. 8). In indicated cases a complete filling of the stomach is done, after this procedure, and the usual method of examination is followed.

PRECAUTIONS AND ADVANTAGES

Precautions.—1. Compression must be carefully applied to avoid excessive pressure.

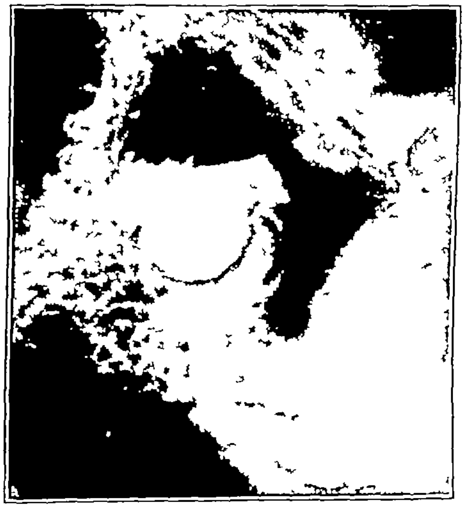


Fig. 6.—A diverticulum of the descending portion of the duodenum.

2. Care must be exercised to avoid interpreting normal variations in the mucous membrane as pathologic.

Advantages.—The advantages of this method might be summarized as follows:

1. It demonstrates more clearly the usual lesions, giving a better conception of the type of lesion, extent of involvement and the treatment indicated in gastrointestinal disease.

initiated into it That danger is the danger of perforation How real a menace is that?

Dr. P G Boman Duluth, Minn With regard to the number of cases that have been proved at operation The cases of gastric ulcer on the lesser curvature, the greater curvature, the pylorus, the posterior wall, with the exception of the one high up on the posterior wall, and approximately 50 per cent of the duodenal ulcers have been proved at operation I have particularly made it a point to study the specimens with reference to the mucous membrane change surrounding the ulcer and comparing this with the appearance of the roentgenogram I do not profess at all to be an expert in this type of diagnosis After seeing the work done by Åkerlund and Berg I feel like a novice I do feel however that it has improved the accuracy of gastric duodenal diagnosis With regard to Dr Eusterman's reference About a year ago I reported a series of five cases of perforation following gastroduodenal roentgen examinations Since the introduction of the compression technic I have not had a case of perforation nor has there been any indication that I might have one. As I mentioned under "precautions" one must use care in the amount of compression used especially in certain cases I believe that there is a potential danger if great compression is applied in the penetrating type of ulcer

PRIMARY CARCINOMA OF THE URETER *

P E McCOWN MD
INDIANAPOLIS

The rarity of primary neoplasms of the ureter and the great difficulties offered to accurate diagnosis, especially in the case presented here has stimulated me to review the reported cases and to present data which, I hope, will aid in the early diagnosis of this condition Early treatment is necessary to save the lives of these patients, since these tumors have widespread and rather early metastases

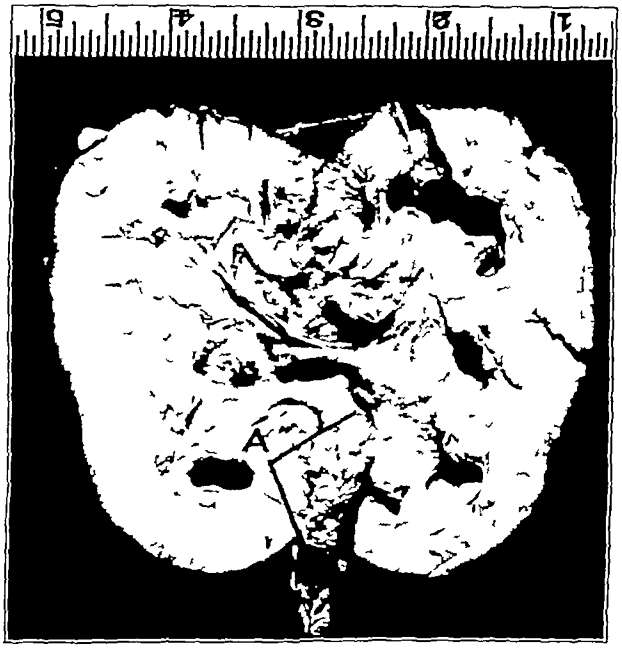
There is no symptomatology that is of any special aid in the diagnosis of this condition A review of the literature on this subject discloses that the diagnosis of fifteen of these cases was made at the autopsy table, in only eight or nine clinical cases was the true condition suspected, and in only three cases was the diagnosis made before operation

The first case report, that of Wiesing and Blix,[1] was made in 1878, and not until that of Davey,[2] in 1884, was it again mentioned in the literature The first summarizing report of Richter,[3] in 1909 disclosed eleven cases Since that time reviews have been made at intervals by Spiess,[4] 1915, Judd and Struthers,[5] 1921, Meeker and McCarthy,[6] 1923, Kretschmer, 1924, and the last summarizing report by Richard Glas,[8] in 1926

Meeker and McCarthy reported thirty-three cases, including their own However it is necessary to eliminate that of Hoffman, as it is a duplicate of a case demonstrated by Finsterer[9] in 1915 Thus, Meeker and McCarthy reported thirty-two cases, to which must be added that of Papin[10] in 1923, Zobel[11] in 1923, Kretschmer[7] in 1924, Mraz[12] in 1924, Crance and Knickerbocker[13] in 1924, Paul Blatt[14] in 1926, Richard Glas[8] in 1926, Posner[15] in 1927, Scheele[16] in 1927, Player[17] in 1928 and Volante[18] in 1928, making a total of forty-three cases of primary malignancy of the ureter, to which I add the following

A white man, aged 45, an official, was referred, Oct. 14, 1925, by Dr Robert M Moore, because of low function and microscopic hematuria The family history was irrelevant. For five months the patient had suffered from headaches and general malaise, which sent him to Dr Moore for a general examination

Dr Moore found him to be asthenic and slightly obese. The patient had not had any physical exercise for twenty years, because of some roentgen burns to the feet. The roentgen treatment had been administered for some type of skin condition



Lines converging to A indicate extent of ureteral carcinoma. Note hydronephrotic pelvis and calices.

The patient reported that his appetite and his habits were good with the exception of a very small intake of fluids He had nocturia one or two times His nose, throat and eyes were pronounced normal by an ophthalmologist and a nose and throat specialist The head, neck and chest were normal The apex beat of the heart was heard at the fifth interspace along the nipple line and no murmurs were heard. The abdomen was normal except that it was easy to palpate the lower pole of the left kidney which did not seem enlarged The extremities were normal except for the old roentgen burns on the feet

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* Read before the Section on Urology at the Eigthieth Annual Session of the American Medical Association Portland Ore July 10 1929

[1] Wiesing J P and Blix C Cancer of Ureters Hygiea **60** 468-476 1879

[2] Davey R. Excision of Left Kidney Brit. M J **2** 757 758 1884

[3] Richter J *Carcinome primitif de l urétere droit* Ztschr f Urol. **3** 93 1909

[4] Spie P D *Die primar epithel Tumoren des Nierenbeckens* und des Ureters Centralbl f allg Path. u. path. Anat. **26** 553 618 1915

[5] Judd E. S and Struthers J E. Primary Cancer of Ureter Review of Literature and Report of Case J Urology **6** 115 (Aug) 1921

[6] Meeker L. H and McCarthy J F Primary Carcinoma of Ureter Report of Case with Review of Literature J A. M A. **81** 104-109 (July 14) 1923

[7] Kretschmer H L Primary Carcinoma of Ureter with Report of Case and Review of Literature Surg Gynec. Obst. **38** 47 51 (Jan) 1924 J Urology **11** 573-579 (June) 1924

[8] Glas Richard Primary and Metastatic Carcinoma of Ureters Wien. klin Wchnschr **39** 1145 1149 (Sept. 30) 1926

[9] Finsterer Ein Tumor des linken Ureter Wien. klin Wchnschr **27** 718 1915

[10] Papin Neoplasme de l uretere J d urol **17**: 325

[11] Zobel O H Zentralbl f Path u. path. Anat. 1925 Leipzig 1923

[12] Mraz J Z Primary Carcinoma of the Ureter J Urology **12** 49 (July) 1924

[13] Crance A M and Knickerbocker H J Primary Carcinoma of Ureter Report of Case, J A. M A **82** 1930 1932 (June 14) 1924

[14] Blatt Paul Surgery of Ureteral Carcinoma Wien klin Wchnschr **39** 1130-1132 (Sept 30) 1926

[15] Posner H L. Primares Ureterkarzinom (Primary Carcinoma of Ureter) *Monatschr f Geburtsh u Gynak.* **75** 86 90 (Nov) 1926

[16] Scheele K Beitrag zur Rontgendarstellung des primaren Ureter karzinoms (*Contribution to the Roentgen Picture of Ureteral Carcinoma*) Fortschr a. d. Geb d Rontgenstrahlen **36** 825 828 (Oct.) 1927

[17] *Player L. P Urol & Cutan Rev* **32** *7 (July) 1928*

[18] Volante F Primary Carcinoma of the Ureter Arch. Ital di urol **4** 105 132 (Dec.) *1927*

Examination of the nervous system showed that the pupils and knee jerks were normal, there was no Babinski reflex The Wassermann reaction was negative Chemical analysis of the blood was normal

Cystoscopy showed a normal bladder, but the catheter on the left side was obstructed at 20 cm and no urine could be obtained The urine flowed freely from the right kidney

A roentgenogram of the kidneys, ureters and bladder did not show any stones The left kidney seemed slightly larger than the right An attempted pyelogram of the left side showed opaque fluid running back along the ureteral catheter from the point opposite the transverse process to the third lumbar vertebra A tentative diagnosis of stricture at the ureteropelvic junction was made Repeated attempts at dilation all failed and, each time that the ureteral catheter was passed to this obstruction hemorrhage followed which was considerably more than one would expect from traumatism of ureteral stricture.

My conclusions were that I was dealing with a probable ureteral tumor or a renal and ureteral tumor, and an operation was recommended

Jan 19, 1926, through a lumbar incision a retroperitoneal nephrectomy was done On liberation of the adhesions around the kidney pelvis, a mass was found in the ureter just below the pelvis, which was about as thick as an index finger Owing to the fact that in a previous case of papilloma of the renal pelvis it was necessary at a later date to do a ureterectomy the ureter was liberated and sectioned about one-half inch above the bladder During the operation no evidence of extension was found and the wound was closed around a rubber drain, the patient returned to his bed in good condition The following day evidence of circulatory failure appeared and the patient died on the third day following the operation with a diagnosis of circulatory failure. An autopsy could not be obtained

Examination of the specimen showed a papillary carcinoma in the upper third of the ureter, without any evidence of metastases or implantations along the ureter, as so frequently occurs in papillomatosis of the kidney pelvis Near the lower end of the ureter was a contraction, which clinically seemed to be a stricture and which had caused some difficulty in the passing of a catheter into the ureter during the treatment stage

Of the forty-three patients, twenty-one were females and twenty-two males The oldest patient was 89 (Troupet-Gueniot [19]), the youngest 35 (Finsterer [9]), and one patient was 80 (Richter [3]) There were three patients from 70 to 79, twelve from 60 to 69, nine from 50 to 59, eleven from 40 to 49 and four from 35 to 39

The right ureter was involved in nineteen cases and the left ureter in twenty-four cases The neoplasm was reported in the upper ureter in five cases, lower ureter in twenty-seven cases, middle ureter in six cases, diffuse in one case, center and lower in one case, multiple in one case, and entire in one case, that of McCarthy

TYPE OF TUMOR

The papillary type of carcinoma is the most common, as has been found in carcinoma of the kidney pelvis, there being twenty-one cases Squamous cell carcinoma was reported five times, medullary carcinoma, two times (Kretschmer reports medullary carcinoma in five of the thirty-five cases reported), and carcinoma solidum, two cases, the remainder being reported simply as nonpapillary carcinoma The size of these tumors was given as that of a cherry, walnut, pigeon egg, finger and thumb In one instance it was reported as having filled half of the pelvis (Hektoen [20])

In the data reviewed, I was able to find the report of calculus three times, but Kretschmer [7] found five cases in which stone was reported, those of Davey,[2] Metcalf and Stafford,[21] Paschkis [22] and Ziromi [23]

The degree of malignancy in this condition is illustrated by the finding of its extension to the rectum, seminal vesicles, sacrum and vagina, one case each It extended to the bladder in six cases Schmitt's [24] case showed involvement of the eleventh dorsal vertebra, the case of Spiess [4] showed involvement of the third lumbar, Adler's [25] case showed metastases in the fourth lumbar vertebra, Hektoen's [20] case showed the intersurface of the ilium eroded, metastases were found in the liver in seven instances, in the lung in four cases, in the pararectal glands in one instance, and in the retroperitoneal glands in six cases

The duration of symptoms from the cases reviewed was from five weeks to fourteen years Hematuria was the most common symptom, it being reported thirty-one times, and as a number of these cases were found at autopsy, it is possible that the symptom of hematuria may have been overlooked in the report Kretschmer states that Adler,[25] Van Chapellan,[26] Hektoen, Toupet and Gueniot,[19] Wiesing and Blix [1] make definite mention of the absence of hematuria in their cases

Pain, the next most common symptom, was described as being in the kidney, sacrum, hip, thigh, diffuse abdominal, one-sided abdominal, upper and lower abdominal, and the inguinal region Thus, it may be seen that there is nothing characteristic about the symptom pain that could be of much assistance in the diagnosis

Tumor was reported as having been felt eighteen times, whereas final analysis showed hydronephrosis reported thirty-two times The clinical diagnosis of tumor of the ureter was made in nine of the forty-three cases Other clinical diagnoses were tumor of the rectum, cystitis, calculus, obstruction of the ureter, stricture of the ureter and various types of renal neoplasm It will be seen that accurate diagnosis from the history and ordinary physical examination is practically impossible The cystoscope revealing papilloma protruding from the ureter orifice has been helpful This occurred in the cases of Gerstein,[27] Finsterer,[9] Paschkis,[22] Judd,[5] Meeker,[6] Posner [15] and Player [17] The fact that rather profuse bleeding occurs from the catheter in meeting an obstruction in the ureter also is a strong indication of a possible ureteral tumor in case stone can be eliminated

Unfortunately, the x-rays may not give much assistance since, in the majority of instances, as in my own case, there was a complete occlusion and reflux of the pyelographic mediums along the ureter Roentgenograms in these cases have been interpreted as defects in the ureterogram, stenosis of the ureter, hydronephrosis and, in Aschner's [28] case, calculi of the kidney Other clinical diagnosis, such as pyonephrosis, carcinoma of the kidney and papilloma of the kidney, have been made It seems to me that anything like an accurate diagnosis will be reached, as in my own case, only by exclusion

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[19] Troupet and Guéniot Cancer de l orifice ureteral du bassinet et de l uretère Bull Soc anat. de Paris **73** 678 1898

[20] Hektoen Ludvig Medicin June, 1899 abstr Rev d sc. med. de Hayem 1896 p 650

[21] Metcalf and Stafford Carcinoma de l uretère avec un calcul logé dans la portion pelvienne, Am J M Sc. January 1912

[22] Paschkis R Primarer Tumor des Harnleiters Wien klin Wchnschr **23**: 361 1910

[23] Ziromi G Cancer primitif de l uretère droit Ann d mal d org génito-urin **1** 81, 101 1909

[24] Schmitt, E C Primary Carcinoma of Ureter J Cancer Res **1** 461 (Oct.) 1916

[25] Adler L. Beitrag zur Kenntniss der primären Tumoren des Ureters Monatschr f Urol **10** 120-142 1905

[26] Van Chapellan Carcinom des Ureters Beitr z. klin Chir **99** 138 1916

[27] Gerstein K. Ein Fall von primaren Krebs der rechten Ureterenmundung Inaug Diss. Kiel May 1902

[28] Aschner P W Primary Tumors of the Ureter Surg. Gynec Obst. **35** 749 (Dec.) 1922

My patient was practically symptomless, afebrile and with no history indicative of pyelitis or urinary infection Repeated roentgenograms of the kidney, ureter and bladder certainly eliminated stone and showed the ureter without kink as far as the catheter reached, also a normally shaped kidney There was no history of tuberculosis, and a clean bladder mucosa was found Free hemorrhage was produced by ureteral catheterization, such as one would not suspect from manipulation of a kink or stricture Finally, the fact that I [29] had had a case of papillary epithelioma of the kidney pelvis with secondary implants in the ureter which bled freely led me to the conclusion that I had such a case, involving the ureter, producing obstruction with a possible kidney pelvis involvement

The treatment in most instances has been nephroureterectomy Involvement of the ureter orifice will require removal of a surrounding block of bladder wall Papin [10] in his case resected and joined the severed ends of the ureter with circular stitching Such repair is liable to stricture formation, and Legueu suggests the implantation of the central end into the bladder, if possible, when resection is feasible In view of the fact that papillomatous tumors are prone to metastasize by implants below the original level, total ureterectomy would seem advisable when this type of tumor is encountered

In summing up, it would seem that primary carcinoma of the ureter is a disease that is rare its vague symptomatology making diagnosis difficult One should keep this condition in mind in the meeting of obstruction in the ureter It should be treated early, since metastases are frequent and widespread

521 Hume-Mansur Building

ABSTRACT OF DISCUSSION

Dr. F P Johnson, Portland, Ore. The rarity of ureteral tumors is striking when compared with those of the bladder and renal pelves It is interesting in this connection to note that embryologically the renal pelves, ureters and vesical trigon being derivatives of the wolffian duct, are mesodermal in origin, while the remainder of the bladder and the greater portion of the urethra derivatives of the allantois, are of entodermal origin Certainly tumors of the walls of the bladder and the urethra are far more common than primary growths of the trigon, ureters and renal pelves It would seem, therefore, that the entodermal epithelium is more susceptible to tumor formation than that of the mesodermal Functionally there is this difference the bladder epithelium undergoes a greater degree of stretching, there being a certain slippage of cells, one over the other, on distention of this organ The ureter, being supplied with longitudinal folds and not serving the purpose of a reservoir, under normal conditions never distends to the extent of flattening its epithelium The renal pelvis, however, not being supplied with folds, and serving the purpose of a reservoir to some extent, probably lies between the bladder and the ureter in this respect. The existing relative frequency of these tumors is established from this point of view It is again established if infection is considered as an etiologic factor for we must admit the greater frequency of cases of cystitis followed next by pyelitis and last by ureteritis Finally, the total surface area of the epithelial lining of the renal pelves, ureters and bladder may be considered as a possible explanation A bladder distended to 500 cc. has approximately 302 square centimeters of area, two ureters each 27 cm long and dilated to 5 mm have a surface area of 84 square centimeters, and two normal renal pelves have approximately 78 square centimeters This is a ratio of bladder to renal pelves to ureters of 100 to 28 to 26 As this would lead us to expect four bladder tumors to one each of the renal pelvis and ureter, we may discard this idea at once as being inadequate for the explanation of the rarity of renal pelvis and ureteral tumors

Dr B A Thomas Philadelphia During the past year we have had an opportunity to study and operate on two patients with so called malignant papilloma of the lower end of the ureter The first patient, a man, consulted us because of hematuria, and cystoscopy revealed a papilloma about 3 cm in diameter, overlying and partially obstructing the ureteral orifice After two or three fulgurations, all visible evidence of the tumor was destroyed, displaying a somewhat enlarged ureteral orifice. Three months later the patient reported in accordance with instructions, and again cystoscopy revealed a reformation of the tumor, growing apparently from the ureteral orifice, but not as large as previously This led us to suspect the presence of tumors of the upper urinary tract, and ureteropyelographic examination showed a tumor the size of a pigeon s egg occupying the lower end of the ureter about 3 cm above the orifice. The upper ureter and kidney showed no filling defect. Accordingly, the bladder and lower end of the ureter with the tumor were resected and the ureter was reimplanted in the bladder Subsequently the patient developed a pyelitis, then a pyelonephritis, necessitating a secondary nephrectomy, following which he has been symptomless and has regained his former health The second patient was also a man, complaining of hematuria Cystoscopy revealed the elimination of bloody urine from one ureter Bilateral ureteropyelography revealed a filling defect of the lower end of the ureter, near its juncture with the bladder No other filling defects were apparent higher up in the ureter or kidney Again the bladder and lower end of the ureter were resected on the affected side and the ureter was reimplanted in the bladder This time no complications arose, and the recovery was uneventful In these cases there is always the possibility, in the presence of cystitis, of an ascending infection up the implanted ureter, which may result in a kidney condition requiring surgery and necessitate secondary nephrectomy or the ureterovesical anastomosis may break down, resulting in a suprapubic fistula, requiring either further transplantation of the ureter or nephrectomy In the matter of diagnosis, it is imperative to determine whether there is any tumor higher up in the ureter or kidney If this is the case, nephro ureterectomy and partial resection of the bladder constitute the operation to be done. In other cases, typified by the cases cited in which the tumor is limited to the vesical portion of the ureter, resection of the ureter and bladder and reimplantation of the ureter into the bladder is the operation to be performed, although secondary nephrectomy may become necessary

Dr William F Braasch, Rochester, Minn It is peculiarly fitting that Dr McCown should bring up the subject of tumors of the kidney and ureter for discussion before this section, since it was about six years ago that he read a paper before this section on tumors of the renal pelvis Up to that time pelvic tumors had been considered something of a rarity, but after the publication of his paper many cases were described and I have no doubt that this paper will call forth reports of many tumors of the ureter which have escaped the facile pens of urologists in the past. The clinical diagnosis of ureteral tumor may be quite difficult. It will first be necessary to differentiate between tumor of the ureter and the various other conditions which may cause ureteral obstruction, such as stone, blood clots, stricture, ureteral granuloma, papillomas and metastases from renal neoplasms Primary tumors of the ureter occur more frequently in the lower third than in the upper The clinical recognition of tumors in the upper ureter may be difficult when occlusion of the lumen is complete If there is sufficient space in the ureter to permit the ureterogram to outline the filling defect the character of the deformity may permit of recognition. With direct catheterization the character of the obstruction met by the ureteral catheter may be suggestive of neoplasm The catheter coming in contact with the neoplasm will frequently cause a marked degree of hematuria The urogram may be quite normal save for a moderate degree of sacculation of the lower ureter at the site of the tumor and to our surprise the upper portion of the ureter and pelvis may be practically normal save possibly for minor dilatation confined to the calices Localized filling defects without any other deformity must be differentiated from blood clots, it being borne in mind that there may be both neoplasm and blood clots It is of the greatest importance to differentiate between primary tumors of the ureter and metastasis from tumors in the renal pelvis If the pelvis can be outlined, the true condition can usually be differentiated, since pelvic neoplasm almost invariably causes recognizable deformity In recent years I have observed a number of localized granulomas of the ureter which may closely simulate neoplasm in every respect A specimen removed through the cystoscope may be the only method of differentiation The treatment of tumors of the ureter is necessarily surgical We would hardly dare to employ radium or fulguration through the cystoscope

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[29] McCown, P E Papillomatous Epithelioma of the Kidney Pelvis J A M A. 75 1191 1197 (Oct. 30) 1920

Dr L P Player, San Francisco Last year I reviewed the literature and reported a case which I think brought out two or three points that I wish to stress In the first place, the complaint was hematuria of three years' duration The patient complained of jaundice occurring irregularly over a period of about two years On cystoscopic examination we found two small tumors in the bladder, one situated at the ureteral orifice, the other in the dome of the bladder The one in the dome of the bladder was fulgurated, that in the ureteral orifice we subjected to biopsy A small specimen was sent to Dr Rusk of the University of California, who diagnosed a papilloma We could not pass a ureteral catheter more than 10 cm on the affected side Indigo carmine appeared normally from the good side, and there was no return from the opposite side The question of diagnosis came up later when the patient returned with recurrent hematuria I could not pass a catheter without causing a great deal of bleeding The type of bleeding was not peristaltic, but just a steady stream of blood. Through the catheter I could not inject any opaque medium and could not make a pyelogram Plain roentgen examination showed evidence of enlarged kidney on that side We did nephrectomy and ureterectomy and on pathologic study of the specimens found a primary carcinoma of the ureter and hydronephrosis Bleeding, nonperistaltic in character, and the fact that a papilloma in the bladder may be a metastasis of a carcinoma in the ureter are the points I wish to stress

Dr A W Hunter, Vancouver, B C Three months ago I had a case of primary tumor of the ureter, with obstruction at the pelvic brim This led me to believe that it was a new growth, or a non-shadow-throwing stone Reexamination at the end of a week to exclude the presence of a blood clot revealed my ability to get by this obstruction and to get a pyelogram of the kidney, which showed no sacculation and did not reveal a tumor at the pelvis The tumor was removed and found to be carcinomatous in character In a preceding case seen two or three years ago, the condition is of interest, as the diagnosis was made before operation on a tumor at the lower end of the ureter The patient was a man who weighed about 250 pounds (123 4 Kg), and I was a little slow in operating He seemed to have had about enough operative intervention after I took out the tumor, so I decided to tie off the lower end of the upper portion of the ureter and trust that he would live If he had too much trouble I intended to do a nephrectomy After I had done this I looked up the literature and found I might be overlooking a primary tumor in the kidney with metastasis in the ureter Fortune favored me in that Dr Braasch happened to be in Seattle at the time, and I showed the pyelograms to him, he consoled me in the belief that if I left the kidney in, the man would live It has now been about four years I have called the patient up every three months and so far he remains in perfect health.

Dr P E McCown, Indianapolis As I suspected, this condition is not nearly as rare as it seems from the literature. As Dr Braasch mentioned when I presented a case of tumor of the kidney pelvis there was a rush of cases I think there are about 200 on record now and in 1920 when I reported my case it was the forty seventh or eighth I thought because of the difficulties in diagnosis that it was worth while to call attention to this matter again I wish to thank Dr Johnson for discussing the etiology I did not go into that because it would take too much time in a paper of this description The experience of Dr Thomas has been that of several of the men whose papers I reviewed Furthermore I feel that we should always remember, as Dr Braasch said, that these ureteral papillomas may be secondary to a papilloma of the kidney pelvis, and this should be carefully determined before any decision to operate on the ureter alone is made. The difficulties of diagnosis are great Our patient did not bleed There was rather marked dilatation of the kidney pelvis and of the calices, and evidently it had been a slow closure of the ureter without any infection, which certainly would have called the patient s attention to the kidney condition Dr Player's discussion was of considerable interest I hoped he would mention a condition that is quite unusual, and that is the resistance of the ureteral coat to secondary infection or invasion from the numerous malignant conditions of the pelvic organs, particularly in women It seems to resist external invasions very well In about 500 operations for malignant growths of the pelvic organs, one writer states that he saw ureteral invasion only four times Primary tumors of the ureter are rather rare and may be confused with secondary ureteral tumors transplanted from papillomas of the kidney pelvis

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VIOSTEROL (IRRADIATED ERGOSTEROL) IN TREATMENT OF PARATHYROID TETANY *

JOHN C BROUGHER, M D
VANCOUVER, WASH

In some previous work I[1] found that cod liver oil raised the serum calcium and relieved tetany in parathyroidectomized dogs In a further study cod liver oil and yeast was used to relieve tetany, and because of the favorable results the treatment was applied clinically to three patients and a report[2] was made

Viosterol (irradiated ergosterol), having more potent vitamin D action than cod liver oil, was substituted in the treatment of experimental parathyroid tetany in dogs[3] The results were such that it was then given to the patients previously reported on instead of the cod liver oil Since that time two other patients have been added, so that this report includes five patients who are receiving viosterol Tetany in four of the patients was the result of parathyroid deficiency following subtotal lobectomy Two of these developed tetany soon after operation, while the other two developed symptoms during pregnancy The fifth patient developed tetany after a long illness and gastro-intestinal upset Complete case histories of the first three were given in a previous paper,[2] so only a summary report of these will be given here

REPORT OF CASES

Case 1—Mrs E, aged 36, white had had a subtotal double lobectomy, March 17, 1926 She became restless and uncomfortable, and in the afternoon was seized with twitchings of the face and carpopedal spasm Ten cubic centimeters of calcium chloride was given intravenously for relief From that time on, she had symptoms of tetany and it was necessary to give calcium chloride in doses of from 30 to 60 grains (2 to 4 Gm) daily and parathyroid extract-Collip weekly Even with this treatment she was not free from symptoms

I first saw the patient, Feb 26 1927 The serum calcium was found to be 7 86 mg per hundred cubic centimeters of whole blood she had a pronounced Chvostek reaction and a

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* The viosterol used in this work was kindly supplied by Mead Johnson and Company

* From the Department of Surgery University of Oregon Medical School Portland Ore

[1] Brougher J C The Treatment of Parathyroidectomized Dogs with Cod Liver Oil Am J Physiol 84 583 (April) 1928

[2] Brougher J C The Treatment of Parathyroid Tetany with Cod Liver Oil and Yeast Northwest Med 27 329 332 (July) 1928

[3] Brougher J C The Value of Acterol (Irradiated Ergosterol) in the Treatment of Thyroparathyroidectomized Dogs Am. J Physiol 86 538-541 (Oct.) 1928

positive Trousseau sign, and complained of insomnia, muscle spasm throughout her body, and tingling of the hands and feet

Therapy with calcium and parathyroid extract-Collip was stopped and cod liver oil, 4 drachms (15 cc.) two times a day, and bakers yeast tablets, 5 grains (0 32 Gm) three times a day, were prescribed She improved on this treatment and felt better than at any time since operation In May, 1928, viosterol was substituted for the cod liver oil The dosage used was 4 drops three times a day, and on this amount she seemed to improve and get along better than on cod liver oil In December, 1928, she was again examined carefully and a mildly positive Chvostek sign was present She had increased somewhat in weight but was not myxedematous She was mentally active The finger nails were not as brittle as they had been, and the numbness in her hands and feet was less during her menstrual periods on viosterol than on cod liver oil She noticed that constipation or excitement caused an exacerbation of her condition Whenever this patient was without viosterol for even a day, she noticed the symptoms of tetany recurring

Case 2 —Mrs W , aged 45, a widow, white, was admitted *with a diagnosis of toxic hyperplastic goiter*

May 11, 1926, partial lobectomy was done

May 25, partial lobectomy was done

May 28 the patient was very restless and had a positive Chvostek sign She was given 20 grains (1 3 Gm) of calcium lactate four times a day and parathyroid extract-Collip occasionally until April 15, 1927, when cod liver oil and yeast treatment were instituted At this time the patient had a fairly marked positive Chvostek sign and complained of insomnia and spasms in her hands and feet. The muscles of her forehead also twitched considerably at times, especially during her menstrual periods She improved on cod liver oil, and the serum calcium was 10 mg

In May, 1928 viosterol was given in a dosage of 4 drops daily This completely prevented any disturbing symptoms of tingling in the toes or hands, restlessness, or spasm of any muscle In March, 1929, the patient went without viosterol for a few days but she began to feel quite nervous again and cramping was noticed in the hands, feet and muscles of the throat and larynx At the time of this report she is in good physical condition and is still taking viosterol

Case 3 —Mrs X aged 30, white entered Multnomah County Hospital, Feb 9 1928 in a spastic state of tetany She was seven and one-half months pregnant. Six weeks previous to this spastic tetany she had observed that her hands were numb and would cramp after she had been working Three days before entering the hospital she had had headache, hyperesthesia about the cheeks, paresthesia about the lips, and twitchings in the muscles about the eyes and mouth Hot flashes passed over her body, and she perspired profusely Soon her arms and legs became numb and cramped painfully These cramps were inter*mittent in nature until spastic tetany ensued She was first* given calcium chloride intravenously, and later parathyroid tablets one-tenth grain (6 mg) and calcium lactate, 15 grains (1 Gm), three times a day

February 12 the patient was given cod liver oil, 4 drachms (15 cc), twice a day No more tetany occurred and she was discharged, February 14 She was readmitted, March 16 and delivered of a full term male child From March 16 to 19 she received no cod liver oil and again developed symptoms of tetany At this time the blood coagulation time was ten minutes, two days after she again took cod liver oil the blood coagulation time was only six minutes July 1, 1928 the patient was given viosterol, 6 drops twice a day, and on this amount was free from tetany during lactation Since the period of lactation, she has still found it necessary to take viosterol daily in the same dosage however, she is able to go without it for a few days at a time

Case 4 —Mrs A, aged 31, white, had a subtotal double lobectomy in March, 1918 *A few hours after the operation* she became very restless and noticed numbness in her face and extremities, associated with painful muscle cramps, which were quite generalized For six days she could not sleep except under the influence of morphine During this time she also had difficult and rapid breathing, and her temperature was high Eating, swallowing and talking were much disturbed

After the patient left the hospital the attacks of tetany came on in varying frequency of from two weeks to two months apart, and during her menstrual periods tetany was very severe No diagnosis of her condition was made for five years, her only relief was a hypodermic. In 1923 the case was finally diagnosed as parathyroid tetany, and for two years she was given calcium and parathyroid tablets They afforded her partial relief but she could not say that she was free from symptoms

When I first saw her, she was seven months pregnant and, because of some nervousness, was taking parathyroid tablets, one-twentieth grain (3 mg) and calcium, 5 grains In spite of this medication she complained of numbness in her face, scalp, hands and feet, flexion of her forearms, and equinovarus spasms These attacks were painful and tetanic in nature, not convulsive

In June, 1928, she was given cod liver oil, 4 drachms, twice a day, in place of the calcium and parathyroid tablets On this therapy she became free from symptoms within a few days and had no evidences of parathyroid deficiency during either *gestation or lactation After four months of cod liver oil* therapy she was given, instead, 4 drops of viosterol twice daily and was free from all symptoms of tetany until March, 1929, when she had a severe attack of influenza, which brought on the symptoms again The dosage of viosterol was increased to 20 drops twice a day and the tetany was alleviated

At the time of this report the patient is taking only 6 drops of viosterol and is clinically in good condition

Case 5 —Miss T , aged 28, white, developed symptoms of tetany following extensive resection of the intestinal tract In June, 1923, she had a curettage In July she was having fever and abdominal pain Appendectomy was performed the right tube and part of the ovary were removed, and a general peritonitis was drained In December she had an obstruction, and 9 feet of intestine was resected In the following June, four more feet was short circuited by anastomosis Since these operations, she had had a constant and painful diarrhea of watery material and masses of mucus

Since the resection of her intestine she had had repeated attacks of tetany with carpopedal spasm painful spasms in other muscles, and rigidity She had also complained of burning and tingling of the face and extremities It is possible that the rapid emptying of the shortened intestinal tract had something to do with a calcium deficiency

In November, 1928 she was found to have a positive Pool or Schlesinger s sign and a negative Chvostek sign She was given 6 drops of viosterol twice daily in addition to the 15 grains of calcium she had been getting, and it seemed to relieve her greatly, as she was less nervous and irritable and slept better

The patient has been taking the viosterol daily for a year now and feels that it benefits her a great deal in relieving the tingling and numbness in the extremities as well as the painful cramps which develop in the muscles if she goes without it *The serum calcium has increased from* 6 7 mg to 12 mg on this therapy The patient also states that she has severe spells of vomiting if she does not take the viosterol It seems that *the food does not enter her stomach, which may be due to* cardiospasm

COMMENT

Viosterol has been found to raise the serum calcium and alleviate tetany in adults having a parathyroid or calcium deficiency

Gleich and Goodman [4] reported three cases in which the administration of viosterol markedly increased the blood serum calcium in a few days Furthermore, it promptly stopped the convulsions in infants who were in a tetanoid state

Stern [5] reported a case in a woman, aged 36, who had suffered from chronic parathyreoprival tetany for fifteen years following partial removal of the thyroid Six weeks of vitamin D treatment in the form of viosterol sufficed to render the patient objectively and subjectively symptom free

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[4] Gleich M and Goodman S Irradiated Ergosterol in the Treatment of Tetany New York State J Med 28 1398-1399 (Dec 1) 1928

[5] Stern A Zur Therapie der parathyreopriven Tetanie mit Vigantol, Deutsche med. Wchnschr 54 1292 (Aug 3) 1928

CONCLUSIONS

Four patients who developed a parathyroid deficiency after bilateral subtotal lobectomy were relieved of tetany by the administration of cod liver oil and subsequently viosterol Two of these patients did not develop tetany until pregnancy A fifth patient who developed tetany after an extensive intestinal resection was benefited by the use of viosterol

Arts Building

THE NEUROPSYCHIATRIC PROBLEM IN THE U S VETERANS' BUREAU*

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LOS ANGELES

The Veterans' Bureau is the largest of the independent branches of the federal government, the director being responsible to the President (table 1) To it is delegated the responsibility for all activities having to do with medical care, and the treatment, compensation and insurance of veterans of the World War Of the total cost of $439,000,000 for operating the Veterans' Bureau in 1928, a little less than $46,000,000, or 10 5 per cent, was expended for the hospital and dispensary care of beneficiaries

Table 1—*Expenditures During the Fiscal Year 1928*

Expenditure for medical care in dispensaries including salaries	$ 10 697 080 17
Expenditure for hospital services including salaries	35,107 024 09
Expenditure of central office	9 000 428.69
Compensation	181 709 605 82
Term insurance (disability and death insurance)	120 770,802 24
Adjusted compensation (bonus)	45 417,562 54
All other general expenditures	36,304,635.38
Total	439 157 199 63

Table 2—*Available Beds and Patient Load in Government, State and Civil Hospitals for the Treatment of Bureau Beneficiaries with Neuropsychiatric Disease*

	U S Veterans Bureau Hospitals		Other Government Hospitals		Total Government Hospitals		State and Civil Hospitals	Grand Total	
Year	Beds Available	Patients	Beds Available	Patients	Beds Available	Patients	Patients	Beds Available	Patients
1920	1875	1363	7	7	1882	1370	3556	5438	4926
1921	2735	2568	1406	1295	4141	3863	3636	7777	7499
1922	3890	2911	1858	1803	5748	4714	4517	10265	9231
1923	4567	3647	2171	1979	6738	5626	3777	10515	9403
1924	5704	5119	2215	1956	7970	7075	2800	10770	9875
1925	8614	7433	2214	2054	10828	9487	2652	13480	12139
1926	9071	8490	2417	1695	11488	10185	2417	13905	12602
1927	9498	9081	1870	1417	11368	10498	2250	13618	12748
1928	10633	10044	1868	1393	12501	11437	1620	14121	13057

HOSPITAL FACILITIES

The bureau is operating forty-nine hospitals located in various parts of the country (table 2) Most of these are of modern construction and all have up-to-date equipment Of the total number, seventeen are especially equipped to care for mental cases while facilities are provided for a limited number in some of the hospitals for medical and surgical patients As indicated in table 2, the number of bureau beneficiaries with neuropsychiatric disease has increased from 4,926 in 1920 to 13,057 in 1928, and the number of beds in veterans' hospitals for this type of case during that time has increased from 1,875 to 10,633 A certain number of beds in hospitals operated by other branches of the government are available These factors have made it possible not only to take care of the increased number of patients but to reduce the number hospitalized in state and civilian institutions under contract from 4,517 in 1922 to 1,620 in 1928

At various sessions of congress the statutes granting hospitalization have been liberalized until at the present time practically any ex-service man is eligible for hospital treatment Recent legislation has provided for a $15,000,000 hospital building program, and it is anticipated that within a few years it will be possible to care for all beneficiaries in government institutions

HOSPITALIZATION OF BUREAU BENEFICIARIES WITH NEUROPSYCHIATRIC DISEASE

Table 3 indicates that the number of admissions, transfers and discharges of bureau patients hospitalized for neuropsychiatric disease has decreased since 1923 On the other hand, the number of deaths has increased slightly and the number of patients remaining under treatment has increased considerably as the result of an accumulation

Table 3—*Movement of Bureau Patients Under Hospitalization for Some Form of Neuropsychiatric Disease Fiscal years 1923-1928*

Fiscal Year	Admissions	Transfers and Discharges	Deaths	Patients Remaining
1923	14 095	14 066	330	9 191
1924	12,119	11 170	268	9 461
1925	16 210	12,507	858	11 905
1926	12 489	11 595	448	12,220
1927	11 490	11 116	408	12 463
1928	11 464	10 704	414	12 839

ADMISSIONS OF PATIENTS WITH NEUROPSYCHIATRIC DISEASE DURING 1928

In reviewing table 4, it will be noted that the readmissions are greater than the admissions There are a number of reasons for this situation (1) the facility with which patients are discharged from bureau hospitals, no legal procedure being necessary, (2) the urgent demand for hospital beds, and (3) the tendency of the medical service to parole or discharge as many patients as possible so as to give them an opportunity to adapt themselves to community and home life

The principal types of diseases for which bureau patients were admitted for hospitalization were paresis, schizophrenia, the psychoneuroses, manic-depressive insanity, and a group of nervous and mental diseases such as tabes dorsalis, epidemic encephalitis, neoplastic diseases of the brain and cord, and various types of paralysis

DISCHARGES OF PATIENTS WITH NEUROPSYCHIATRIC DISEASE DURING 1928

A review of table 5 indicates that there were 11,118 bureau patients discharged during 1928 following hospital treatment for some neuropsychiatric disease Of this number 2,659 were hospitalized for a psychoneurosis, 2,020 had been hospitalized for schizophrenia, 512 for paresis, 329 for manic-depressive insanity, and 632 for various forms of neuritis

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* Read before the Section on Nervous and Mental Diseases at the Eightieth Annual Session of the American Medical Association Portland Ore, July 10 1929

† Dr Crossman died, June 21 1929

WAR EXPERIENCES AS ETIOLOGIC FACTORS OF NEUROPSYCHIATRIC DISEASE

The importance of war experiences as etiologic factors in the development of the neuroses and psychoses has been discussed from time to time However, a brief review of some of the salient points may be of value

The psychoses as well as the neuroses observed in the U S Veterans Bureau may be classified as follows (1) those cases which had their inception during the war period or were precipitated by war service, (2) postwar psychoses and neuroses considered by law as of service origin and known as "presumptive cases" The first group includes the conditions which developed during the war period and in which there was a probability that war experiences were the predominant factors in their etiology, recurrence or exacerbation The second group, namely, the presumptive cases, comprises those in which there is an element of doubt as to the role of the war experience in the etiology of the disease, so that congress passed legislation giving the ex-service man the benefit of the doubt

TABLE 4—*Admissions of Neuropsychiatric Patients to All Hospitals by Classification of Disease and Type of Admission During Fiscal Year 1928*

Classification of Neuropsychiatric Disease	First Admission	Readmission	Admission by Transfer	Total
Psychosis				
Traumatic	8	13	7	28
Senile	13	9	4	26
With cerebral arteriosclerosis	8	7	5	20
Paresis	230	161	102	493
With cerebral syphilis	29	16	8	53
With Huntington's chorea	1		2	3
With brain tumor	2			2
With other brain or nervous diseases	4	6	2	12
Alcoholic	50	41	10	101
Due to drugs and other exogenous toxins	4	2	2	8
With pellagra	4	4		8
With other somatic diseases	23	45	19	87
Manic-depressive	103	165	63	331
Involutional melancholia	2	1		3
Schizophrenia	611	929	765	2,305
Paranoia or paranoid conditions	5	10	1	16
Epileptic	15	80	31	126
With psychopathic personality	11	49	22	82
With mental deficiency	17	49	20	86
Undiagnosed	116	85	17	218
Without psychosis				
Constitutional psychopaths	93	307	27	427
Drug addiction	18	35	5	58
Epilepsy	139	290	15	464
Mental deficiency	58	94	8	160
Psychoneuroses and neuroses				
Hysteria	311	584	23	918
Neurasthenia	263	425	7	695
Neurosis anxiety	58	101	6	165
Neurosis (otherwise unclassified)	27	39		66
Psychasthenia	225	399	17	641
Psychosis hysterical	6	14		20
Trance		3		3
Neurosis traumatic	26	44		70
Other neuropsychiatric diseases	1,534	1,530	44	3 108
Under observation neuropsychiatric diseases	352	375	24	751
Total	4,286	5,912	1 256	11 454

C S Read[1] maintains that the development of a neurosis depends on three factors heredity, early individual experiences, and some precipitating cause During the world conflict, with its horrors of modern warfare, the precipitating factor, that is, the military experience, was so predominant that the influence of heredity as well as the past individual experiences were overshadowed

It might be well to state that in the experience of the bureau very few of the neuroses were caused by explosions or warfare gases The term "shell shock" used during and immediately after the war for these neuroses was really a misnomer in that a large number of these conditions were the result of emotional factors However, in either case the real etiologic factor was inherent in the individual

In considering the causative factors of the psychoses of warfare, one is impressed with the complete transformation which the soldier underwent during military service During this period there was a subjugation or self-effacement of the individual, abnegation of free thought and conduct, and the difficulty of adjusting oneself to the rigid military discipline These forces, together with a psychopathologic predisposition, tended to produce mental reactions of an abnormal kind These reactions were increased in extent and number by associated factors, such as the breaking of social ties, family care, financial reverses at home, and the dread of future incapacity or loss of life

From 1917 to 1919 inclusive, 313,200 men were discharged from the army, navy and marine corps for various disabilities, of which number *78,930*, or *25.2* per cent, had some form of neuropsychiatric disease

TABLE 5 —*Discharges from U S Veterans' Hospitals of Neuropsychiatric Patients by Type of Disease During Fiscal Year 1928*

Classification of Neuropsychiatric Disease	
Psychosis	
Traumatic	25
Senile	23
With cerebral arteriosclerosis	25
Paresis	512
With cerebral syphilis	64
With Huntington's chorea	3
With brain tumor	6
With other brain or nervous diseases	17
Alcoholic	102
Due to drugs and other exogenous toxins	8
With pellagra	10
With other somatic diseases	91
Manic-depressive	329
Involutional melancholia	5
Schizophrenia	2 020
Paranoia or paranoid conditions	20
Epileptic	113
With psychopathic personality	93
With mental deficiency	90
Undiagnosed	102
Without psychosis	1 187
Psychoneuroses	2 659
Tabes dorsalis	151
Hemiplegia	182
Multiple sclerosis	116
Neuritis	672
Paralysis agitans	83
Paralysis	149
All other neuropsychiatric conditions	2 206
Total	11 118

It has been noted that while in a large number of instances the neuroses ceased when active warfare was at an end, the psychoses continued to develop

TYPES OF TREATMENT

During recent years more emphasis has been placed on the treatment of psychotic patients, and it is the aim of the bureau to provide medical attention for its beneficiaries which will be second to none

Occupational Therapy—This is used as an adjunct therapeutic measure in the bureau with most excellent results Occupational therapy[2] is graded into (1) habit training, (2) crafts and shop work, and (3) industrial activities, such as agriculture in its various forms and work about the station This type of treatment is prescribed by a medical officer after a study of the patient's industrial background, his present mental and physical condition, and his likes, dislikes and adaptability, with a view of giving that type of occupational therapy which will result in maximum benefit. In veterans' hospitals it has been observed that various occupational therapy measures have eliminated many psychotic upsets and have had a tendency to keep within normal bounds introverts and mischief-making extroverts. The patient who begins in the habit-training class is advanced as soon as is practicable to the simple form of shop work and then to a type of activity requiring more coordination and concentration; as soon as possible he is sent to the dairy, poultry yard or some outdoor activity where he will be doing a real man's job.

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[1] Read C S Military Psychiatry in Peace and War London 1920

[2] Kefauver H J The Vocational Aspect of Occupational Therapy Occup Therap 5 1 (Feb) 1926

In the treatment of psychotic patients, two objectives are sought: hospital adjustment and social adjustment.[3] The attainment of the first objective is hastened by suitable occupational therapy and recreational activities. It is the aim to make the patients interested, satisfied and efficient members of the hospital community in which they live. In order to accomplish this, proper work, sufficient exercise and recreation are provided. When the patient has made a hospital adjustment, he is on the way to social adjustment. Those who have progressed so that parole is being considered are given occupations which so far as practicable simulate life in the community. A study of the reaction of the patient to various forms of occupational therapy assists in determining the advisability of parole.

Physical Therapy.—The use of physical methods in the treatment of disabled service men in the army and navy hospitals was so successful that special attention has been given to this branch of therapy in the bureau. In neuropsychiatric hospitals, hydrotherapy and physical exercise are especially emphasized, while electrotherapy, actinotherapy and massage are used to a lesser extent. At each hospital there are trained technicians who, on the prescription of a medical officer, administer these forms of treatment. The hydrotherapy installations consist of continuous baths, which are of value in the quieting of disturbed patients, and control tables with needle shower baths, with which either tonic or sedative treatments may be given.

In the large hospitals, physical directors are on duty. These employees supervise graduated exercises in classes and, when indicated, in individual patients. Various recreations are used for therapeutic purposes, it having been found that many patients can be induced to enter into competitive games such as baseball, handball, volleyball, tennis and track athletics when interest cannot be otherwise aroused.

Social Work.—The services of psychiatric social workers are being increasingly utilized by the bureau in relation to diagnosis, treatment and follow-up (table 6). It is the usual procedure to have a complete social study made of each patient admitted to the hospitals specializing in the treatment of neuropsychiatric patients, in order to have an understanding of his social setting, the emotional relationships present, the events that have influenced the development of his personality from infancy, and the factual or delusional basis for his present ideas and interpretation of the events that have led up to his hospitalization. With social data of this kind the regional office dispensaries are finding it unnecessary to hospitalize claimants for observation in some cases; in others the observation period in a hospital is markedly shortened. During the year 1928, 6,475 complete social studies were made.

Preparole investigation of the home situation to learn and, if necessary, to modify family attitudes, standards of living, financial resources and possibilities for recreation and employment are being made in an increasing number of instances when a patient's return to the community is under consideration. This not only expedites his safe return, thereby encouraging the family to agree to and cooperate in his having a trial visit but makes possible a more satisfactory life outside the institution with less liability of requiring early readmission. The supervision of patients in the community is the phase which presents the greatest challenge to the group of Veterans' Bureau psychiatric social workers, and they are particularly interested in helping the patients reach an occupational adjustment.

Many of the claimants reside long distances from the hospitals or dispensaries, which makes it necessary that the social worker utilize to the maximum existing social agencies in the community.

The carrying of concepts of mental hygiene and health standards into rural communities constitutes a unique social work contribution by the Veterans' Bureau.

Aside from its more intensive work with paroled patients, the Veterans' Bureau at least once a year has a social survey made of each incompetent beneficiary living in the community and of the 33,787 minor wards of the Veterans' Bureau, that is, children of incompetent or deceased beneficiaries who are receiving compensation on account of the parent's service-connected disease. These are preventive aspects of social work, as they afford opportunity to discover and modify adverse elements tending to precipitate an acute attack, to arrange for early reexamination and treatment in the case of incompetent beneficiaries, and to take prompt action regarding behavior or health problems which may be developing in the children. Table 6 shows certain of the activities of the eighty-three Veterans' Bureau psychiatric social workers during 1928.

Table 6.—*Activities of the Eighty-Three Psychiatric Social Workers from January to December, 1928*

Home visits	13 085
Investigations	
Complete social studies	6 475
Studies of special points	9 063
Preparole	890
Social problems handled (monthly average)	
Personality adjustment	468
Financial	818
Home conditions	421
Employment	221

IMMEDIATE RESULTS OF HOSPITALIZATION

In table 7 are indicated the immediate results of the hospitalization of bureau patients with neuropsychiatric disease. It is noted that of 11,118 patients discharged during the fiscal year 1928, 1 per cent were reported as recovered, 44.26 per cent as improved and 6.83 per cent as unimproved, 3.72 per cent died during hospitalization, and 44.19 per cent were discharged for various administrative reasons.

The reason for the small percentage of recoveries is that bureau physicians are inclined to be conservative in recording the immediate results of treatment and consider patients in the stage of remission as "improved" rather than as "recovered."

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[3] Carr, B. W.: Occupational Therapy for Psychotics, U. S. Vet. Bur. M. Bull. 2: 362 (April) 1926.

LATE RESULTS OF HOSPITALIZATION

For the purpose of ascertaining the late results of treatment, a special study was made of a group of patients hospitalized for neuropsychiatric disease The ultimate benefit from hospitalization is difficult to ascertain unless some follow-up system is in operation at a hospital (table 8) The statistical system in the bureau is such as to lend itself readily to follow-up studies for the purpose of ascertaining the end-results of treatment The bureau hospitals, working as a control group, are in a position to make a more complete follow-up study than any other psychiatric institutions because they are not restricted by state lines, because the bureau is also in contact with the patients or their legal representatives on account of compensation benefits, and because of the social service available in the hospitals and dispensaries

In this investigation a study was made of the hospital records of 2,684 bureau patients whose treatment began prior to June 30, 1922, and who were discharged after being hospitalized for various periods The time covered by this study was from June 30, 1922, to Nov 21, 1928 It was thought that the results of hospitalization over a period of approximately six years should give a reliable index to the results of the institutional care of patients with neuropsychiatric disease In selecting this group of patients, one of the requirements was that the specific diagnosis of the patient continue throughout the period of hospital treatment The majority of the patients under treatment in veterans' hospitals are between 30 and 40 years of age

Table 7—*Immediate Results of Hospitalization for Neuropsychiatric Disease for the Fiscal Year 1928*

	Number	Per Cent
Recovered	111	1 00
Improved	4 921	44.26
Unimproved	759	6.83
Died	414	3 72
All other discharges	4,913	44 19
Total	11 118	100 00

Table 8—*Late Results of Treatment of 2 648 Patients First Hospitalized Prior to 1922 for Some Form of Neuropsychiatric Disease*

	Number	Per Cent
Recovered	16	0 60
Improved	1,358	50 60
Unimproved	868	32 34
Died	280	10 43
Not reported..	162	6 03
Total	2 684	100 00

TYPE OF CONDITION TREATED

At this point it might be well to elaborate briefly on the nature of some of the more common neuropsychiatric diseases encountered in the group of patients under consideration and to attempt to describe the part played by the military service in their cause, clinical course and progress

Paresis—Chavigny is of the opinion that the paretic patient of the war shows a tendency to maniacal and excited states Read was unable to confirm this finding A number of observers have come to the conclusion that the difference in susceptibility in paresis must be due to the individual rather than to a difference in the etiologic organism

The question is often asked whether or not warfare with its stress and strain brings about an increased incidence of this disease, also whether the symptoms evolve more quickly in such circumstances

White is of the opinion that the development of this disease is hastened by active warfare On the other hand, Hotchkiss in his analysis of cases at the Dykebar War Hospital arrived at the opinion that military service did not increase the incidence of this disease

It is a fact, however, that the age incidence of paresis in veterans is somewhat earlier than in the civilian population, which indicates the possibility that the period of incubation is shorter among the military population Furthermore, the data of the bureau hospitals seem to show that, once the disease develops, it progresses more rapidly than do the cases in civil life.

There were 246 patients with paresis in the group of 2,684 patients admitted for hospitalization previous to 1922 Of this number at the end of the observation period none had recovered, thirty-seven, or 15 04 per cent, were improved, thirty-three, or 13 41 per cent, were unimproved, and 176, or 71 55 per cent, had died

In this connection it might be well to say a word or two about the treatment of paresis by "inoculation malaria" The clinical and laboratory observations following this treatment were most favorable The good results were suggested by Matz[4] as being due to the age of the bureau patients (average age 38 years), and the early diagnosis and persistent intensive antisyphilitic treatment, as well as to the excellent care which these patients received in the bureau hospitals The longest period of treatment and observation was forty-seven months and the average was twenty-seven months

Of a group of 346 patients treated by "inoculation malaria" 23 99 per cent were greatly improved, 41 04 per cent were improved, and 22 83 per cent were unimproved, 7 31 per cent showed deterioration, and 3 47 per cent had died In 1 16 per cent, the condition of the patient was not recorded

At a number of bureau hospitals where tryparsamide has been used in the treatment of neurosyphilis, the results obtained have been very encouraging For instance, Neymann and Singleton[5] in a group of cases have found that 50 per cent of the group showed improvement or had recovered They also found that parenchymatous syphilis of the central nervous system responds more favorably to tryparsamide therapy than does the mesoblastic type

Schizophrenia—This disease was one of the most common of the psychoses observed in the army While there are several theories concerning the etiology of schizophrenia, it is our opinion that this condition, with a susceptible patient, may be precipitated by active military service and is the result of maladaptation of the soldier to his military environment

The group studied consisted of 803 patients admitted for treatment previous to 1922 for the various types of dementia praecox Of this number at the end of the observation period, none were reported as recovered, 305, or 37 98 per cent, were improved, 300, or 37 36 per cent, were unimproved, and eighty-three, or 10 34 per cent had died In 115, or 14 32 per cent of the cases, the result of treatment was not recorded

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[4] Matz, P B The Treatment of Neurosyphilis by Inoculation Malaria in the United States Veterans Bureau J Nerv & Ment Dis 68 113 (Aug) 1928

[5] Neymann C A. and *Singleton D E. Therapeutic Results* with Tryparsamide in the Treatment of Neurosyphilis U S Vet. Bur M Bull. 2 435 (May) 1926

Constitutional Psychopathic Inferiority —The patients in this group had some abnormality of the emotional rather than of the intellectual sphere Those under observation in the bureau hospitals showed qualities of marked suggestibility and emotional instability, so that inhibitions to the control of various instinctive impulses were much lessened and abnormal conduct in some form or other manifested itself early in life

One hundred and thirty-nine patients of this group were studied At the end of the observation period none were discharged as recovered, fifty-two, or 37 41 per cent, were improved, seventy-six, or 54 68 per cent, were unimproved, and one, or 0 72 per cent, had died In ten, or 7 19 per cent, the condition on discharge was not ascertained

Epilepsy —Little can be said regarding the part played by the military service in the causation of epilepsy In those instances in which the condition was cured, it was felt that the nature of the disease was functional A number of these cases were due to war injuries and were of the traumatic type.

There were 225 patients in the group On termination of treatment, none had recovered, ninety-seven, or 43 11 per cent, were improved, 116, or 51 55 per cent, were unimproved, and six, or 2 67 per cent, had died In six, or 2 67 per cent, the condition on discharge was not obtained

Mental Deficiency —The condition of mental deficiency was one of the most important with which the recruiting officer, as well as the medical officers in the various camps, had to deal A large number of mental defectives who were taken into the army were not permitted to use a rifle and it was necessary to allow them to perform only simple duties It was found that these individuals broke down quite frequently when the slightest responsibility was placed on them Eleven thousand and three men were discharged from the army, navy and marine corps during 1917, 1918 and 1919 on account of mental deficiency

Colonel Salmon was of the opinion, after the experiences of the World War, that mental defectives should be debarred from the military service Other observers also state that their presence in the military establishment is a menace

It is interesting to note that one of the principal symptoms manifested by these feebleminded soldiers was the wandering spell, which lasted for hours in some instances, the soldier being found away from his unit in a more or less dazed condition Many of these defectives were court-martialed for desertion and often punished when, as a matter of fact, they were totally irresponsible for the acts committed

There were 228 patients with mental deficiency in this group On termination of hospital treatment none had recovered, seventy-nine, or 34 65 per cent, were improved, and 145, or 63 6 per cent, were unimproved In four, or 1 75 per cent, of the cases, the ultimate condition was not reported

ORGANIZATION OF BUREAU WORK

In connection with this discussion of the treatment of neuropsychiatric patients, it may be of interest to speak of certain developments which materially assist in the medical work of the bureau

Medical Council —In order to administer forty-nine hospitals and fifty-four dispensaries properly and efficiently, the medical service decided that it might be well to seek the cooperation and counsel of some of the outstanding men of the profession to guide it in matters of medical policy Accordingly a number of the leading physicians, hospital administrators and statisticians were requested to meet with the medical director and to organize the medical council

The members of the council meet periodically at Washington, D C, for the purpose of advising the medical service on various problems of professional and scientific importance confronting it The members of the medical council are frequently requested to inspect hospitals and dispensaries for the purpose of ascertaining whether or not the work of these activities is done in accordance with accepted medical standards

Diagnostic Centers —In the course of the hospitalization and dispensary care of bureau beneficiaries, conditions were encountered which were difficult of diagnosis or of successful treatment Accordingly it was decided to establish a number of centers to which these problem cases would be sent for diagnosis or treatment The consulting staffs of these diagnostic centers consist of some of the foremost physicians and surgeons of the country

At the present time three institutions of this type are in operation at Washington, D C, Cincinnati and Palo Alto, Calif A fourth diagnostic center is in contemplation and will be located at the Edward Hines, Jr Hospital, Hines, Ill, near Chicago

Research —In 1925 the medical service established a research department, the object of which was to administer, foster and encourage research in the hospitals and dispensaries of the bureau Through the research department the medical service makes studies of available medical data in the bureau and measures therapeutic results and accomplishments in the hospitals and dispensaries in the treatment of various diseases Through this department also the medical service investigates the standards and definitions for clinical improvement in medical centers and applies these to bureau work

The staffs of the hospitals and dispensaries are encouraged to engage in research work so far as their duties will permit The research department of the medical service receives the cooperation and assistance of the research group of the medical council

Postgraduate Schools —In 1928 the medical service of the bureau established two postgraduate schools—one at the U S Veterans' Hospital in Palo Alto, Calif, and the other at the U S Veterans' Hospital in Washington, D C Instruction at these postgraduate schools is continuous throughout the year and is given by the members of the consulting and resident staffs of the two hospitals

U S Veterans' Bureau Medical Bulletin —On account of the large amount of clinical material found in the bureau hospitals and dispensaries and also for purposes of education, the medical service established a monthly journal, the *Medical Bulletin* Each full-time medical officer is required to contribute at least one article a year to the *Bulletin* This journal also serves as a medium for reporting the results of research work conducted in the various hospitals and dispensaries of the service

SUMMARY AND CONCLUSIONS

1 The experiences of modern warfare undoubtedly have precipitated many psychoneurotic and, to a lesser degree, psychotic attacks, and also have hastened the development of paresis, in many instances causing a more rapid course of the disease

2 Among psychotic cases intensive professional treatment, with personal attention to each patient, not only is most effective in bringing about improvement of the condition but results in a diminution of the period of hospital stay

3 With proper soil, schizophrenia apparently develops to a considerable extent as the result of the stress, worry and rigid discipline of modern warfare

4 Bureau psychoneurotic patients are more effectively treated in most instances in dispensaries than in hospitals

5 The bureau physicians are inclined to be conservative in reporting the result of hospitalization It is their tendency to report cases in remission as "improved" rather than as "recovered "

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ABSTRACT OF DISCUSSION

Dr. Theodore Diller, Pittsburgh I have been touring Europe for the last three summers Three hospitals that I visited impressed me very much, one in Hungary, one in Copenhagen and the other in Barcelona All of these hospitals had one thing in common exceedingly attractive grounds or gardens and surroundings I have seen several hospitals in France, delightfully situated, one in particular at autumn was exceedingly charming, resembling a fine old-fashioned home, and it has been in operation 400 years I have been impressed with the ugliness of many of our hospitals in cities The beautification of the grounds and surroundings has been wholly neglected too often We live in a beautiful country, we meet in a city where trees and flowers are abundant and where they are greatly appreciated by those who are at home and those of us who come here from a distance. I make a plea for taking advantage of these beautiful things for our hospitals They have their effect on the patients, on nurses and on the friends of patients I hope that the authors can tell us that the veterans' hospitals are well situated and are in beautiful surroundings

EVALUATION OF THE MOTILITY OF THE SPERMATOZOA

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For years the motility of the male sex cells has been considered the chief or even sole criterion by which to judge the fertility of the male It is too often forgotten, however, that motility is not even an inherent attribute of the spermatozoa, and Schucking[1] believes that in some animals with external fertilization the sperms, themselves not motile, may be brought to the ovum by external circumstances and then fertilize it This is contradicted by others,[2] but the fact that such a difference of opinion can occur shows that motility alone must not be rated too highly There are other characteristics of the sperm cells which are just as important as motility, as I[3] have brought out before in previous articles

In animals with internal fertilization the spermatozoa, of course, need motility to reach the ovum, but the degree of motility present under the microscope in any one particular instance must not be interpreted as giving a direct clue as to the fertilizing power of the sperms Loss of motility, or lessened motility of the sperms, is of course of great importance, but only if carefully repeated examinations can show that such disturbed motility is really present A sluggishly motile or even nonmotile spermatozoon is not necessarily a dead or useless cell In the testis the sperms are normally nonmotile, and even in the ejaculated semen a nonmotile cell may be merely dormant On the other hand, the fact that the cell is motile does not in itself mean that its fertilizing power is undisturbed As in the ovum the fertilizability, so in the spermatozoon the fertilizing power, gradually decreases until the sperm cell is practically powerless to produce fertilization even if it is still motile This has been shown by numerous experiments (Wolf,[4] Ivanoff,[5] Walton, Hammond and Asdell,[6] Hammond and Asdell,[7] Walton[8]) Furthermore, I have seen highly abnormal cells actively motile

In examining the fresh sperm cells in my cases, I used first a number 6 Leitz objective and a 10 Leitz ocular, and then a Leitz 1/12 oil immersion objective and the same ocular as before I also used the dark field in some instances Never at any time was I able to see any expansion or contraction of the sperm head, as is mentioned sometimes in the literature It is to be admitted that at times expansion and contraction of the sperm head seemed to exist, but close examination always showed that the apparent change in size and shape of the sperm head was due to its turning on its longitudinal or even vertical axis, thus seeming to produce expansion and contraction of the head In addition, the refraction of light caused by the disturbance of the seminal fluid around the sperm head always magnified the apparent size changes of the head While it is true that the sperm head of the starfish after it enters the ovum without its body or tail oscillates from side to side as Chambers[9] has described, there is here also no expansion or contraction of the sperm cell, and the slight motion observed may be explained by chemical or mechanical factors (currents of cytoplasm in the ovum, for example) The observation of Lillie[2] that a contraction of the nereis sperm head takes place after it enters the ovum also has nothing to do with an ameboid-like activity of the sperm head, as the whole process here is more one of simple shrinkage than of any active change in shape As far as the large "sniffing" or "seeking" sperm cell is concerned, it always appeared to me that this was a cell which had lost most of its original tremendous activity, and thus, because it was slowed down, seemed to hesitate and search for some object to attack Such "sniffing" cells are generally not larger than others In fact, no normal semen specimen ever shows many differences in the size of the cells, as will be brought out fully in another paper dealing with the morphology and biometrics of the spermatozoa

In order to determine as closely as possible the value of motility as a criterion of the normality of the semen otherwise, I made extended tables of motility and the duration of motility A study of these tables, which are not presented here, as their main points can be given in a few words, showed what deceptive criterion motility alone may be Some specimens of semen from men with perfectly normal breeding records contained actively motile sperms which remained alive twelve, twenty-four and even thirty hours and more whereas other samples from equally normal men contained only sluggishly motile cells which were nearly all dead apparently after from five to six hours Again, specimens of semen with many palpably abnormal forms, which were always looked for in the fresh specimens, would have very actively motile cells which remained so for a long time. In many instances specimens from the same man obtained and kept under apparently identical conditions would show different degrees of motility. It might naturally be argued that conditions were different, even if they appeared identical, but if such slight variations as escape detection under ordinary circumstances can affect the sperms, too much value cannot be placed on slight changes in motility observed under the microscope. W. W. Williams[10] also believes that motility alone may be a deceptive criterion, since apparently trivial factors influence it. Lewis,[11] in working with boar sperms, regularly found that the sperms of some animals lived longer outside the body than those of others, although he was unable to assign any reason for this difference of behavior.

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[1] Schucking Arch. f d ges Physiol **97**, 1903

[2] Lillie Frank Problems of Fertilization Chicago University of Chicago Press 1919

[3] Moench G L Am J Obst. & Gynec. **13**: 334 (March) 1927 M J & Rec. **126** 94 (July 20) 1927 M Herald March 1928

[4] Wolf J Agr Sc **11** 1921

[5] Ivanoff J Agr Sc. **12** 1922

[6] Walton Hammond and Asdell Verhandl f Sexualforsch **2** 1928

[7] Hammond and Asdell Brit. J Exper Biol **4** December 1926

[8] Walton J Proc Roy Soc. S B **101**: 303 (April) 1927

[9] Chambers R. Proc. Soc Exper Biol & Med. **20**: 137, 1922 J General Physiol **5** 821 (July) 1923

It is of course quite generally true that spermatozoa do not all live equally long outside the body, and curves of the percentage of motile forms at different time intervals give considerable variations in motility. The cause of this is unknown. It is certainly not due to the abnormal forms, as I have seen these live as long as other normal cells in the same specimen, and at times even longer. It seems to me that the whole occurrence is simply one of random sampling. As long as all the sperms in laboratory specimens have to die eventually, some will have to die first, as the conditions cannot be exactly equal for each single cell. I can for this reason also attribute slight significance to the finding of many dead sperm cells in the cervical or uterine secretions, since the death of millions of sperms in these locations must be the normal occurrence.

As far as the actual motion of the spermatozoa goes, I always found this to be flagellate and progressive in addition to rotary about the long axis of the sperm cell. That is, the actual mode of progression was in larger or smaller spirals. It was interesting to note in my specimens the thigmotactic and flocculation reactions[12] of the human sperms. The germ cells would gather around the edge of a drop or radially around the foreign body as though attempting to fertilize it, and remain almost immobile, or rotate only on their long axis, both clockwise and counter clockwise until disturbed, when they would dash off violently in all directions.

In order to test out the various ways in which motility could be affected, I tried out various diluents, as distilled water, salt solutions of varying strengths, including physiologic solution of sodium chloride, and also various dilutions of sodium bicarbonate, dextrose, human blood serum, and numerous chemicals. In every case, with the exception of human blood serum and 2 to 5 per cent dextrose solution, motility was reduced by the diluent. In the last two solutions the sperms remained actively motile even longer than in the natural semen. This seems easy to understand as far as the dextrose solution is concerned, but the explanation in the case of the serum is not quite clear to me as yet and is still under investigation.

By diluting the semen with equal parts of 5 per cent dextrose solution I have been able to observe motility of the sperms for more than fifty-four hours after emission. Such continued motility would seem to contradict Cohn's[13] view that the sperms have only a certain definite amount of energy to expend. One must remember, however, that one never sees all the cells of any specimen actively motile, so that some of those lying motionless may simply be resting.

In adition to the points mentioned, I further investigated whether light or gravitation had any effect on human sperm cells and their motility. However, the cells never showed any difference, whether kept in the dark or in the light, and allowing them to settle also had no effect on their motility, except a purely mechanical inhibitive action. When the cells were released from this inhibition, they again became actively motile.

That change in temperature affects the sperms is of course well known, but I believe that it is generally less well known that the sperm cells are much less sensitive to low than to high temperatures. Specimens which were kept cold, for instance, retained their motility longer than those kept at room temperature, probably because the sperms are more sluggish in the cold and thus use up their store of energy more slowly.

I also tried out the effect of temperature on motility by keeping samples of the same semen specimen (1) undiluted, (2) diluted half and half with 5 per cent dextrose solution, and (3) diluted half and half with physiologic solution of sodium chloride in one case in the icebox, in the second case in the incubator at from 37 to 38 C., and in the third case at room temperature. After eighteen hours the specimen from the icebox showed a few slightly motile sperms in the undiluted semen, and the cells could not be vivified by warming or by adding dextrose. The specimen in physiologic solution of sodium chloride showed no motile forms, and no cells could be made motile. The dextrose specimen, on being taken from the icebox, however, showed about 10 per cent motile forms, and, on being warmed, about 50 per cent of the cells became actively motile. At room temperature, the sperms in the undiluted semen after eighteen hours were nearly all immotile, only a few showing slight motion. The saline solution showed most of the cells actively motile, and the dextrose solution showed practically all the cells normally motile. The specimen kept in the incubator for eighteen hours showed no motile sperms at all, either in the undiluted or in the diluted semen, and the cells could not be revived. Thus my experiments seem to corroborate the general view that the spermatozoon can live only a relatively short time at the temperature it is subjected to in the female genital system. At the same time, the results cannot be transferred directly, since the question of the hydrogen ion concentration plays a role here, too, and the hydrogen ion concentration is not likely to be the same in such different solutions as in the uterus or tubes.

Since cold affects the spermatozoa less than heat, I keep my specimens in the icebox at a temperature of 10 C. but my examinations are always carried on at room temperature. A warmed microscope stage was not used. The latter, in my opinion, is not only cumbersome but useless, since, if all examinations are made at room temperature, conditions remain more or less the same in this respect at least, and comparative results are possible. Furthermore, spermatozoa which die quickly only because they are exposed to room temperature, unless the latter is excessively high, are probably not virile enough anyway to overcome the obstacles necessary to reach the ovum.

Some observers state that the vitality of the sperms from old bucks (rabbits) is lessened and that such cells are more sensitive than those from younger animals[14] In my experiments I have not been able to determine any such relationship to age I have, however, found that poor general health affects motility, one man losing all motility after an attack of influenza and, to date, six months later, not having yet regained it It has been said that frequent intercourse reduces motility This I cannot corroborate Some specimens after repeated intercourse appeared to present a lessened motility, but since other most trivial factors, as described, may influence motility, I did not attach much importance to these observations I can, however, definitely state that in many cases frequent intercourse over a continued period of time did not in any way impair motility, but individual variations again appear to play a role here It is known that some couples may for years have daily intercourse and still have numerous children, whereas other marriages seem to become sterile following sexual overloading

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[10] Williams W W Cornell Vet 17, October 1927

[11] Lewis Oklahoma Exper Sta Bull 96 1911

[12] Dewitz Arch f d ges. Physiol 37 219 1885, 358 1885 1886 Massart Bull de l Acad Roy de Belgique 15 750 Walton Brit. J Exper Biol 2, October, 1924

[13] Cohn Anat. Rec. 21: 530 1921 Biol. Bull 34 167 1918

Whether or not it is true that straight tailed sperms mean that the spermatozoa are alive at the time of emission, on the theory that live cells thrown out in disarray straighten out and dead ones do not, is a question which I cannot answer But one can easily conceive of the tails straightening out, even in dead cells It is known, for instance, that cells with coiled and twisted tails do not by themselves mean dead cells, as I have seen such sperms motile, even though, as a result of the loss of the active lashing of the tail, they moved but slightly and slowly Furthermore, coiled tails may be produced after ejaculation as a result of chemical changes I have been able to produce such twisted tails, for instance, in the majority of the cells of a specimen of semen by diluting it three to four times with distilled water and letting the specimen stand for a short time This is described in detail elsewhere[15]

SUMMARY

It can be said that motility of the sperm cells is a requirement without which, in animals with internal fertilization, pregnancy cannot occur Motility is, however, not an exclusive requirement of the sperms, since other factors are just as important Absence of all motility in repeated, absolutely fresh and uncontaminated semen specimens establishes the cause of the sterility, but the slight changes in motility, as to the degree and length of time the cells remain active, unless such time is unduly short, must be judged very cautiously, as often such changes mean nothing, being due to purely temporary and accidental local conditions

In addition to the examinations of the ordinary fresh specimens, I also tried vital staining of the sperm cells but never was able to learn any more by the use of this method than by the simple examination of the unstained cells Besides, I never felt sure that the stain might not have affected the spermatozoa

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[14] Hammond and Asdell (footnote 7) Sanders J Agr Sc **16**, 1926

[15] Moench G L J Obst. & Gynec **17** 53 (July) 1929

The Art and Science of Medicine—Science is exacting It is interested in diagnosis first, and treatment last That is perfectly proper when it can be done But the unscientific mind does not grasp the idea Most of our patients are wholly unscientific and are looking only for relief Even in cases where scientific methods are used to the best advantage, much can be done to add to the happiness of the patient and his family by the application of art—Gunn, F H Medical Education, *Illinois M J*, December, 1929

BLOOD DEXTROSE DETERMINATIONS

A STATISTICAL COMPARISON OF THE FOLIN-WU METHOD AND THE BENEDICT MODIFICATION OF THE LEWIS-BENEDICT METHOD *

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AND
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That there is dissatisfaction with the present methods of blood sugar estimation is evident from the numerous methods that have been presented, as well as the frequent modifications of each of them The estimation of blood sugar is a clinical necessity that should be carried out far oftener than it is at present, but to do this the method should be simple, reliable and inexpensive in both time and material The amount of blood required should be small, not more than 0 2 cc , preferably 0 1 cc should suffice for a check The clinical use of the patient's veins has so increased for the administration of medication that both patient and physician look askance at the pathologist who asks for blood from the scarred and thickened vessels Having encountered difficulties with Folin's ferrocyanide method partly because of its small range, we decided, preliminary to further study, to compare and ascertain the accuracy of two of the methods for blood sugar estimation most in use

A review of the literature of the past fifteen years reveals a considerable difference of opinion as to the comparative value of the picrate and copper blood sugar methods Baumann and Isaacson[1] note that "the work of the Harriman Research Laboratory investigators raised serious objections to the use of any picric acid method when another procedure is available" Osterberg and Strunk[2] found the new Benedict method the more accurate except in high sugar values While the view has been expressed that creatinine gives five times the color value of an equal weight of dextrose with picrate, Myers[3] observed that the color was equal, and therefore of no clinical import in ordinary samples of blood Oser and Karr[4] found the Folin-Wu method high below and low above the standards Duggan and Scott's[5] determinations showed the Folin-Wu method accurate for from 25 to 275 mg , with the greatest error 1 6 per cent in the upper range They found the Benedict modification of the Lewis-Benedict method accurate within 1 3 per cent inside 25 per cent from the standard used Rothberg and Evans[6] noted that the Folin-Wu method was high up to 484 2 mg of dextrose experimentally determined from 400 mg of actual dextrose content Apparently no paper was based on a statistical study, and indeed most of the figures given in all the papers in the literature are based on more or less numer-

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* Read before the Section on Pathology and Physiology at the Eightieth Annual Session of the American Medical Association Portland Ore July 12 1929

[1] Baumann E. J and Isaacson R L An Adaptation of the Folin and Wu Blood Sugar Method Applicable to Small Amounts of Blood, J Lab & Clin. Med **7**: 357 (March) 1922

[2] Osterberg A E. and Strunk J A Comparison of the Folin Wu and the New Benedict Method for the Estimation of Blood Sugar J Lab & Clin Med **12**: 278 (Nov) 1926

[3] Myers V C Chemical Changes of the Blood in Disease J Lab & Clin Med **5** 640 (June) 1920

[4] Oser B L and Karr W G The Correction of Folin Wu Blood Sugar Values J Biol Chem **67** 319 (Jan) 1926

[5] Duggan W F and Scott E L. A Critical Examination of Four Methods Commonly Used for the Determination of Sugar in Blood J Biol Chem **67** 287 (Jan) 1926

[6] Rothberg V E and Evans F A. Studies with the Folin Wu Blood Sugar Determination J Biol Chem **58** 435 (Dec.) 1923

The tabulated data presented here are also shown graphically for clarity and convenience in checking routine laboratory determinations of dextrose in blood

The formulas are based on the following assumptions (1) small errors are more frequent than large, (2) plus and minus errors are equally frequent, (3) very large errors do not occur

The probable errors of the means of the Folin-Wu method range from ± 0 147585 to ± 0 0168909 in terms of colorimeter readings, which as may readily be seen correspond to very tiny differences in dextrose This very smallness of probable error of the mean definitely points to accuracy in carrying out the determinations This is further supported by the fact that the probable error of any one determination ranges from ± 0 3983208 to ± 0 0585 in terms of colorimeter readings, which values again are so small as to point clearly to accurate procedure Any one determination is probably at or near the mean, but there is one chance in twelve that it may lie at the upper limit and one in twelve that it may lie at the lower limit of the area bounded by the two limit curves The same truth is even more clearly exemplified in the case of the Benedict modification of the Lewis-Benedict method, with probable errors of the means ranging from ± 0 1481 to ± 0 0154381 in terms of colorimeter readings and the probable errors for any one determination ranging from ± 0 514 to ± 0 0534 Thus the errors of operation are shown statistically to be very small and it follows that the wide divergence between experimental and true values can be accounted for only by errors inherent in the methods themselves

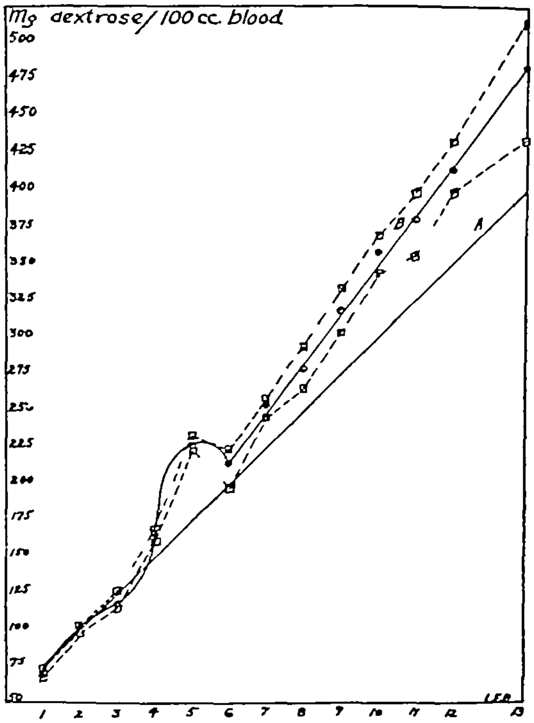

Chart 2 —Folin Wu method *A* actual dextrose content *B* experimental dextrose Low standard 1 to 5 inclusive high standard from 6 on

While the Benedict method checked clinically with the Folin-Wu method in pure dextrose solutions, in blood filtrates other reducing bodies add to the apparent dextrose and this is especially true in certain disease conditions Hence the Folin-Wu method is the more reliable of the two methods It should, however, be used with precaution As shown by the cusp in the curve, the unknown should always be checked against the high standard for blood sugar concentrations in excess of 150 mg per hundred cubic centimeters and in excess of 300 mg greater accuracy will be obtained by dilution of the filtrate and the use of the high standard This further dilution will add to the usefulness of the micromethods based on the Folin-Wu technic, 0 1 cc of blood being used, an amount easily obtained by skin puncture

As shown in chart 2, the Folin-Wu blood sugar method with 200 mg of dextrose gives an average error of reading 6 per cent too high, with a maximum of 12 per cent high and a minimum of 1 per cent low At 400 mg the error of the average reading has increased to 20 *per cent too high, with the maximum* 28 per cent and the minimum 8 per cent high The importance of interpolation of the true reading from the chart is evident, along with the fact that blood sugar readings should not be written beyond the significant figure of the second decimal per cent, or the nearest 10 milligrams per hundred cubic centimeters Generally speaking, a given determination of dextrose in blood should be expressed in terms of the mean value plus or minus such values as bring it within the error range of the limiting curves given in the chart, and then, the true sugar value found by interpolation from the chart and expressed as that value, plus or minus the same inherent error

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ABSTRACT OF DISCUSSION

Dr Victor C Myers, Cleveland I think it would be a good thing if all workers who are going to carry out any determination would first apply principles somewhat similar to those which Drs Pickard and Pierce have applied to the determination of the blood sugar All methods have their limitations, but most workers do not thoroughly appreciate that fact The authors' paper is a good illustration of this point I think that most of those who have worked with the Folin Wu method have appreciated (certainly Dr Folin has) that one should use several different standards if one wishes to obtain the most accurate results, but I dare say that the majority of workers have ignored this fact On that account, probably, a great many results have been reported which were too high because, after all, a clinician is interested chiefly in diabetic blood If he obtains a blood sugar reading that is a little too high, often he will not go to the trouble of preparing another standard and making the determination again, although this is a comparatively easy thing to do I have always felt that it does not matter so much what blood sugar method we use The Folin-Wu method has been used so long now and is so satisfactory that perhaps it should not be abandoned, but we should appreciate that the Folin-Wu *method gives results that are too* high The Benedict modification of the Lewis-Benedict method, which Drs Pickard and Pierce employ, likewise gives results that are too high, probably higher than the Folin-Wu method The figures for the Folin-Wu method are probably about 22 mg above the figures for the true dextrose In practical work, however, one does not care whether one has 100 mg or 80 mg It is merely a scientific affair But we should appreciate that the older methods, and I refer to the Folin-Wu and Benedict (trinitrophenol) methods, do give results that are a little too high Dr Folin and Dr Benedict recently have suggested methods that apparently give readings close to the true blood sugar, but their new reagents are more complicated I do not believe that at the present time I would suggest replacing the Folin-Wu method with either Folin s or Benedict's modification of it I do think that it is important now and then to check over our methods as Drs Pickard and Pierce have done

Dr Leo F Pierce, San Diego, Calif Dr Myers has said that not only are more standards needed with the Folin-Wu method but more methods are needed. It must also be recognized that the interpolation must be made and the results expressed as plus or minus within the natural error that is inherent in the method. Closer results, closer expressions than that, are utterly ridiculous The literature for fifteen years has been simply seeded with statements of the most utterly loose character imaginable When the author says, 'Our curve has been straightened," his statement is distinctly open to question The last thing that Dr Myers mentioned was particularly interesting He suggested that Folin's new method might possibly be better I should like to point out one thing Folin's new method is based on suspending a more or less insoluble precipitate This precipitate is colored It is suspended by means of a protective colloid, and in suspending this precipitate by means of a protective colloid one has particles that are above true molecular dimensions Therefore, one is not truly measuring color but instead is approaching the field of nephelometry Any one who has worked with that realizes the pitfalls and dangers, so that I fear we cannot hope for too much in the way of accuracy from Dr Folin's new method

Clinical Notes, Suggestions and New Instruments

SPINAL DEFORMITY AS CAUSE OF CARDIAC HYPERTROPHY *

William D Reid M D Boston

Finley[1] reported four cases of extreme deformity of the thorax resulting in hypertrophy and dilatation of the heart with cardiac insufficiency Another observer[2] reports the reverse of this sequence in a girl, aged 14, who acquired rheumatic mitral stenosis at the age of 3 and in whom increasing deformity of the spine appeared at the age of 10 years I reported a possible case of the sequence pointed out by Finley, in the first edition of my book.[3]

The case now reported here is, perhaps, more convincing

REPORT OF CASE

History—A girl, aged 16, was admitted to the hospital, May 10, 1928, in an orthopneic, markedly cyanosed condition, with edema of the legs, lower abdominal wall and face.

There had been dyspnea on moderate exertion during the past few months, and occasional attacks of palpitation in the last three or four years Two weeks before entrance the dyspnea had increased, and swelling of the legs, abdomen and face and an unproductive cough had appeared. She had been forced to sit up for the past four nights because of dyspnea

The patient suffered a severe attack of anterior poliomyelitis at the age of 2 years Marked deformity of the thorax and contractions of the limbs had gradually developed since the illness at 2 years of age She had been unable to walk for some years

Physical Examination—The patient appeared poorly nourished and much deformed markedly cyanotic and orthopneic The thorax was markedly deformed with a scoliosis and anteroposterior convexity

The cardiac impulse was weakly palpable in the sixth interspace at the left midaxillary line, percussion showed that the left border of deep cardiac dulness was at the same point. The right border of percussion dulness was 1 inch to the right of the midsternal line. There was a systolic thrill over the apex impulse, and a loud blowing systolic murmur maximal at the apex, audible over the entire precordia There was also a low pitched diastolic murmur at the apex. The action was regular and the rate 120

Moist crepitant rales and dulness were present at both bases and to a lesser degree throughout both lungs The abdomen was distended, a fluid wave was present There was moderate edema of the legs, lower abdominal wall and face

The temperature was 99 6 and respiration 25 The remainder of the physical examination did not elicit any important departures from the normal

Hemoglobin was 70 per cent, the white count was 12 000, with 67 per cent polymorphonuclears, 31 per cent lymphocytes and 2 per cent endothelials

An electrocardiogram showed simple tachycardia with a rate of from 140 to 145, the P-R interval was 0 14 second, the Q-R-S 0 06 second, and P_2 0 3 millivolt, there was right axis deviation at an angle of + 113 degrees This indicated the normal mechanism of the heart beat at an accelerated rate. Preponderating hypertrophy was probably present

Course—The patient did not improve under treatment, the pulse rose to 140 and the respiratory rate to 60 Death ensued twenty-four hours after admission

Autopsy—The pathologic diagnosis was bronchopneumonia (bilateral), kyphosis, hypertrophy of the heart, chronic passive congestion of the liver and kidneys and ascites

The heart weighed 255 Gm The pericardium was normal The myocardium appeared normal in color and in consistency The right ventricular wall showed marked hypertrophy and was practically the same size as that of the left ventricle they both measured about 1 cm in thickness The valves were normal

Microscopically, moderate chronic fibrous endocarditis and myocarditis were apparent.

COMMENT

My former case[3] in a man, aged 51 with auricular fibrillation and congestive heart failure, did not appear convincing because of the obvious possibility that other factors might have caused the cardiac disease. This 16 year old girl however, presented a picture more closely resembling that described by Finley[1] A presumptive diagnosis of mitral stenosis and therefore of rheumatic heart disease was made but was not confirmed by the autopsy Cardiac hypertrophy and congestive heart failure were present. The disclosure of pneumonia was a surprise, it is emphasized that examination of the chest was limited because of the grave condition of the patient

The autopsy notes unfortunately do not describe the course of the aorta in this girl, so it is impossible to state whether the aorta or the pulmonary artery was unduly kinked or narrowed, as noted by Finley[1] in his cases

The association of cardiac hypertrophy and dilatation is not new Finley[1] points out that there is practically no mention of it in English and American medical literature but there are a number of foreign reports It was recorded as long ago as 1828 Bachman found that, in 268 necropsies of patients with high grade scoliosis or kyphosis, 66 per cent showed hypertrophy and dilatation of the heart. For a further review of the literature and a discussion of the mechanism by which spinal deformity induces cardiac changes, the reader is referred to Finley's[1] article.

Although skeptical at first, I am now of the opinion that high grade spinal deformity may have a deleterious effect on the heart There is therefore additional reason for efforts to prevent or lessen such deformities The possibility of the development of cardiac injury should be emphasized to the orthopedists and patients should be encouraged to undergo the prolonged treatment necessary to prevent high grade spinal deformity

SUMMARY

In the case reported here, cardiac hypertrophy and dilatation were associated with marked spinal deformity This association appears to have been largely ignored in Anglo-Saxon medical literature.

The possibility of the development of serious impairment of the heart is an additional reason for the adequate use of orthopedic measures to prevent or lessen high grade deformities of the spine

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* From the Evans Memorial Hospital and Boston University School of Medicine

[1] Finley F G Spinal Deformity as Cause of Cardiac Hypertrophy and Dilatation Canad M A J **11** 10 (Oct.) 1921

[2] Lee, H G Rotarolateral Curvature of the Spine Secondary to Hypertrophy of the Heart New England J Med **199**: 78 (July 12) 1928

[3] Reid W D The Heart in Modern Practice, Philadelphia J B Lippincott Company 1923 p 426

VARICELLA GANGRENOSA DUE TO BACILLUS DIPHTHERIAE, WITH A CARDIAC COMPLICATION

John Zahorsky M D St Louis

The condition reported here is exceedingly rare, and the case with its complications offers some interesting suggestions from a diagnostic point of view The patient was seen several times in consultation with Dr H E Markwort.

C K, a boy, aged 7 years, well nourished, with healthy, educated and fairly well to do parents, living in good surroundings in a modern home with plenty of sunshine, was taken sick, June 18, 1929, with chickenpox The lesions were rather profuse but the general symptoms were mild Before this illness he had often complained of pains in his legs, had a poor appetite and seemed a little pale He had not had any attack of sore throat, coryza or bronchitis for several months There had been no nasal discharge of any kind

Three days after the onset of the chickenpox, two blisters appeared on the back of the neck and healed with simple antiseptic applications About four days after the onset a large bleb appeared over the middle and outer side of the right leg This enlarged and became black. The varicellar lesions over the rest of the body healed normally The child, however, had a slight fever every day, was languid and drowsy, and had no appetite On the fourteenth day he vomited several times

I saw him first, July 4, on the fifteenth day of his illness I was struck at once by his pallor and general prostration The temperature was 100 2 F Physical examination showed a large necrotic ulcer of the right leg about 1½ inches (38 mm) long, covered by a black crust This was surrounded by a pale, moist areola one-half inch (12 mm) wide The skin in several places still showed some crusts of convalescent chickenpox

The inguinal glands on the right side seemed larger than on the left. There was no general adenopathy The spleen was not palpable, but the liver seemed enlarged The nose and the throat were perfectly normal, without discharge or exudate Considerable weakness of the left arm and leg was present, suggesting a nerve lesion The pulse was feeble but not unusually rapid The heart impulse was located in the mammillary line On auscultation the heart showed a typical gallop rhythm. The urine contained albumin, many cells and a few casts

The weakness of the arm and leg, and the condition of the heart did not improve in two days, and this suggested to me that a diphtheritic poison was the cause A culture of the ulcer was taken by Dr Markwort and sent to the city bacteriologist The culture showed the presence of diphtheria bacilli, and a virulence test demonstrated that they were extremely virulent We injected 15,000 units of diphtheria antitoxin intramuscularly The heart was stimulated with caffeine and small doses of nux vomica

The necrotic ulcer improved, but not the general symptoms The heart did not improve and the pulse became slower (86) but the first sound was feeble and reduplicated and the second sound accentuated Death was preceded by a sudden high temperature and convulsions No necropsy was made

This curious syndrome, a polyneuritis accompanied by a myocarditis, which suggested that the gangrenous ulcer might be diphtheritic, emphasizes a practical lesson in every case of varicella gangrenosa a dose of diphtheria antitoxin should be injected on the first appearance of the symptoms I am well aware that in only a few cases has *Bacillus diphtheriae* been found in the gangrenous lesions of varicella, but the serum can do no harm even in cases not caused by diphtheria

In a fatal case of gangrenous chickenpox reported by Alexander Joe[1] *Bacillus diphtheriae* was isolated from the nose during life The baby, aged 13 months, had several gangrenous areas on the skin following chickenpox A blood stained discharge appeared from the nose and 2,000 units of diphtheria antitoxin was administered The gangrene became worse and death ensued A culture made from the necrotic areas after death demonstrated the presence of a virulent strain of *B diphtheriae* The case reported here is singular in that no nasal or faucial diphtheria was present in the patient or in any members of the family

536 North Taylor Avenue.

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[1] Joe Alexander Brit J Dis Child 25 111 (April June) 1928

Council on Pharmacy and Chemistry

REPORTS OF THE COUNCIL

The Council has authorized publication of the following report

W A. Puckner Secretary

FARASTAN NOT ACCEPTABLE FOR N N R

Farastan is the name under which the Farastan Company, Philadelphia, markets a preparation of iodine and cinchophen claimed to be mono iodo cinchophen, a "new chemical complex," containing approximately 33 6 per cent of iodine The preparation is recommended for use in "Arthritis Rheumatoid and Neuritic conditions" It *is claimed as the main advantage* of Farastan that when the preparation *is administered the* 'Iodine *is set free as such, never as hydriodic acid*" If this is true, it would have no advantage, since iodine is converted into iodide before it is absorbed, and it may be deleterious, if the iodine is liberated rapidly enough to produce local irritation

There is no evidence that the routine use of cinchophen and iodide in fixed proportions (or in any proportions) is desirable or rational Usually, the conditions that require cinchophen do not require the simultaneous administration of the iodides, and vice versa If they are used together, the dose of the iodide must be adjusted according to other principles than that of the cinchophen It appears particularly undesirable and even dangerous to encourage the routine prescribing of cinchophen, which should be used only for short periods, with an iodide *compound, which must be continued over long periods If the* administration of iodide together with cinchophen should be indicated or desirable, these can be given separately

The Council declared Farastan unacceptable for New and Nonofficial Remedies because it is an irrational preparation marketed with unwarranted therapeutic claims

ANTISTREPTOCOCCUS SERUM OMITTED FROM N N R

For some years the Council has been questioning the value of antistreptococcus serum preparations These products have been retained in New and Nonofficial Remedies with the caution that on the basis of clinical reports there is perhaps justification for the use of the serum in streptococcus infections, but that there is no scientific basis for it. To obtain an estimate of the esteem in which antistreptococcus serum was held by clinicians, Dr Emil Novak at the request of the Council sent a questionnaire to a number of surgeons, gynecologists and obstetricians The Council considered the report prepared by Dr Novak on the basis of the information which he obtained (report on Antistreptococcus Serum, The Journal, Jan 16, 1926, p 189) and endorsed its publication In consideration of the opinions contained in Dr Novak's report, the Council decided to retain antistreptococcus serum preparations in New and Nonofficial Remedies provisionally

When considering the reacceptance of products in 1928, the Council again questioned the value of antistreptococcus serum preparations and voted that unless new and favorable evidence (aside from the Novak report) became available, all streptococcus serum preparations should be omitted from New and Nonofficial Remedies with the close of 1929 Since no such new evidence has become available, the Council voted to confirm its action and to omit all streptococcus serum preparations as follows Antistreptococcic Serum (Gilliland Laboratories, Inc.), Antistreptococcic Serum, Polyvalent (Lederle Antitoxin Laboratories), Antistreptococcic Serum (Eli Lilly & Co), Antistreptococcic Serum, Purified and Concentrated (Lilly), Antistreptococcic Serum, Polyvalent (H K. Mulford Company), Antistreptococcic Serum (National Drug Company), Antistreptococcic Serum (Parke, Davis & Co), Antistreptococcic Serum Squibb

COMMITTEE ON FOODS

The following products have been accepted as conforming to the rules of the Committee on Foods of the Council on Pharmacy and Chemistry of the American Medical Association These products are approved for advertising in the publications of the American Medical Association and for general promulgation to the public They will be included in the book of Accepted Foods to be published by the American Medical Association

Eugene F Du Bois.	Lafayette B Mendel.
W McKim Marriott	H C Sherman
	Morris Fishbein Chairman.

BORDEN'S EVAPORATED MILK

Manufacturer—The Borden Company New York City

Definition—Evaporated milk is defined by the United States Department of Agriculture as 'The product resulting from the evaporation of a considerable portion of the water from milk, or from milk with adjustment, if necessary, of the ratio of fat to nonfat solids by the addition or by the abstraction of cream It contains not less than seven and eight tenths per cent (7 8%) of milk fat, nor less than twenty-five and five tenths per cent (25 5%) of total milk solids provided, however, that the sum of the percentages of milk fat and total milk solids be not less than thirty three and seven tenths (33 7%) "

Composition—Borden s Evaporated Milk has the following average composition

Fat	7 85%
Protein	6 88%
Carbohydrates	9 67%
Ash	1 55%
Total solids	25 95%
Water	74 05%

Process of Manufacture—Whole milk produced from healthy cattle under carefully supervised sanitary conditions is brought to the condensery Immediately on delivery it is subjected to thorough inspection The necessary laboratory tests are made and it is then standardized so as to conform to the required state and federal standards The first step in the transformation of raw milk into evaporated consists in heating it either by injecting live steam into the vat of milk or by passing the milk through a heated coil The temperature of heating is from 200 to 212 F and the time required must necessarily be varied, as this is an important factor which affects the physical qualities of the milk after it has been sterilized After the preheating has been completed, the hot milk is drawn into a vacuum pan where it is concentrated until about 60 per cent of the water is removed This is done at a low temperature varying from 120 to 135 F From the vacuum pan the milk is pumped through an homogenizer under a pressure of approximately 3,000 pounds This serves the purpose of reducing all of the fat particles to a small size thereby preventing the separation of the butter-fat after sterilization The homogenized milk is then cooled and transferred to a refrigerated storage tank Further laboratory tests are made to make certain that it meets the required standard It is then run by means of mechanical filters, into the can and immediately sealed and sterilized The sterilizing process consists of placing the cans in a steam sterilizer where they receive a temperature of from 234 to 245 F for a period varying from twenty to thirty minutes As the physical condition of the product is dependent on the time and temperature of sterilization, care must necessarily be exercised in conducting the sterilizing process The cans are immediately chilled, withdrawn from the sterilizer, and placed in storage for a minimum period of ten days Each can is then examined to determine whether any 'leakers' are present A 'leaker" is known in the trade as a can in which the seams have been imperfectly made, thereby permitting bacteria to enter after sterilization. To prevent the marketing of such cans they are examined after the required storage period of ten days All cans found to be satisfactory are then suitably labeled, packed and ready for the market

Uses—Borden's Evaporated Milk is advertised for infant feeding to the medical profession only and in women's magazines for household use and in making milk convenient for cooking It is claimed that the milk is clean and sterile that it resembles breast milk in ease of digestion because it is so homogenized that the fat never causes disturbances as in ordinary cow's milk and that it produces fine flocculent curds It is claimed that it contains the natural fats, proteins, lactose, minerals and all vitamins normally present in milk except vitamin C.

CREAM OF WHEAT

Manufacturer—Cream of Wheat Company, Minneapolis

Definition—Cream of Wheat is a product made entirely from wheat. The raw material is taken from the first break rolls of the flour mill, is purified, repurified heat treated or sterilized to remove the possibility of the germination of any insect life, and packed in triple sealed and double-wrapped heavy cardboard containers, in which form it reaches the consumer s kitchen It consists of the endosperm of the wheat, with only so much of the bran and germ as it is impossible to remove in the milling and purification process

Uses—1 Rich in energy content 2 Easy digestibility The manufacturer claims 'School tests show that the child who eats a hot cereal breakfast is better prepared mentally and physically to do good work

GERBER'S STRAINED VEGETABLE PRODUCTS

Manufacturer—Gerber Products Division, Fremont Canning Company, Fremont, Mich

Brands—Gerber s Strained Spinach Strained Carrots Strained Green Beans, Strained Peas, Strained Prunes, Strained Tomatoes and Strained Vegetable Soup

Process—Specially selected vegetables, steam pressure cooked, sterilized at high temperature and specially packed

Uses—The manufacturer claims By excluding the air and cooking under steam pressure without water we are able to effect a greater conservation of the rich mineral salts and vitamin elements than is possible when the same vegetables are cooked in the presence of oxygen in open vessels Particularly this conserves the important vitamin C, in which pasteurized milk is deficient and which vitamin is so susceptible to heat destruction when oxygen is present Gerber s Strained Vegetable Soup is based on a professional formula and contains barley, rice, carrots, spinach beef, celery tomatoes and peas Affords the variety required for a balanced vegetable feeding schedule rich in tooth, bone and body building vitamins "

THE NEW PETTIJOHN'S

Manufacturer—The Quaker Oats Company, Chicago

Composition—Whole wheat grain

Process—Is made by steaming and flaking a choice wheat which has a tender bran The bran is included with it in unground form—the form in which bran is most effective, and the thorough cooking in the home so softens and moistens the bran that it does not harm the sensitive intestinal tissues

Uses—Contains all the nutritive elements of whole wheat It contains carbohydrates for heat and energy protein for building and repair of bone and muscle, the various mineral salts, iron for the blood, lime for the bones and teeth and vitamins

POST'S BRAN FLAKES WITH OTHER PARTS OF WHEAT

Manufacturer—Postum Company, Inc. Battle Creek, Mich

Patents—These cereal flakes are made under the patent to Jonathan K. Lippen, number 1483515, Feb 12 1924 The trade mark Post s Bran Flakes with other parts of Wheat (registered U S Patent Office) indicates the manufacture of Postum Company Incorporated

Composition—Bran flakes with other parts of wheat deliciously flavored with malt syrup and salt.

Uses—Combines the advantage of wheat bran, including essential mineral elements in a nourishing and appetizing food Provides phosphorus iron and vitamin B, recognized dietary essentials proteins and carbohydrates, affording high food value in easily digestible form.

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SATURDAY, FEBRUARY 15, 1930

THE UNDERNOURISHED CHILD OF SCHOOL AGE

Pathology, etymologically, is the science of suffering The content of its subject matter has become much broader than the word itself It includes not only those conditions which may cause suffering but also all deviations from the normal Before it is possible to say that a state is abnormal or pathologic, it is necessary to determine what is normal For actual morphologic tissue changes, this determination is relatively easy, but for states that are not associated with detectable tissue alterations it is necessary to determine the normal mean together with the deviations above and below the mean which may be considered to fall within the range of normal variation When the deviation exceeds the accepted limits of variation, it remains to be determined whether a condition of morphologic or functional abnormality exists

Excessive deviation beyond the limits of variation accepted as normal for weight in relation to height, age and sex is frequent Height, age, sex and race are important in determining the normal weight standards Other factors may play a part, heredity seems to be one such factor Overweight or underweight of degrees great enough to be considered abnormal may be associated with disturbed endocrine functioning There remain, however, many examples of overweight and underweight that cannot be explained by endocrine dysfunction, heredity or any of the factors that affect the normal variations of weight

In children of prepubertal school age, underweight and an evident state of undernutrition are not uncommon and are often a source of worry to parent, teacher and physician Investigation of the individual case may show the undernourished state to be due to chronic infection, to poor diet or to improper food habits In a considerable proportion of undernourished children, a cause for the nutritional state cannot be detected They do not exhibit anatomic abnormalities other than those that are a part of or the result of the undernourished state itself Do they reveal any functional abnormalities to which the nutritional state may be ascribed? The Elizabeth McCormick Foundation of Chicago has been engaged for a number of years in practical work, in the public schools and in the homes, aimed at overcoming the undernourished condition of school children Many children who had no physical defects that might cause undernutrition failed to make a satisfactory gain in weight Study of such refractory cases was undertaken by the Nelson Morris Institute for Medical Research of Chicago, at the suggestion of and with the financial support of the foundation The results of this investigation, which was planned to cover a five year period, have been presented in a series of papers by Chi Che Wang[1] and her co-workers The series of communications is an important contribution to our knowledge of the energy and chemical metabolism of the child of school age

Thorough physical examination by the staff of the Sarah Morris Hospital for Children, to which the children were admitted for prolonged and continuous study, excluded physical abnormalities other than the condition of underweight The children taken for study were selected from those in whom the workers of the Elizabeth McCormick Foundation had found it impossible to bring about a gain in weight A group of normal children, studied in the same way as were the underweight ones, served as controls for the latter One of the earliest results of the investigation, and one that was repeatedly confirmed throughout its course, was that the children, although they had proved refractory to the methods pursued in school and in the home, could be made to show a progressive and satisfactory gain in weight under the conditions of the investigation The increase in weight, however, required such constant supervision by a trained dietitian of each meal taken by the child as to make it appear doubtful whether the result that may be obtained is worth the effort that must be expended to bring it about, since serious nutritional abnormalities could not be detected during the course of the further work

There was no significant deviation in the basal metabolism of the underweight children The metabolic rate of the normal controls, when calculated according to height, was found to be from 10 to 15 per cent higher than the Benedict standards That of the undernourished children was slightly lower than that of the normals A similar but somewhat greater decrease in basal metabolism has been found by others in the normal adult during starvation or fasting The absorption of calcium and nitrogen was as good in underweight as in normal children The retention of calcium was slightly higher and that of nitrogen markedly higher in the underweight children than in the normal controls Underweight children appeared to have a better utilization of nitrogen than did the normal ones, in that the former did not have a negative nitrogen balance as readily on a low protein intake as did the normal children The undernourished children made a much better and more rapid gain in weight on a high than on a low protein intake Creatinine excretion, when calculated according to body weight, was normal and varied directly with the body weight All the children excreted creatine, the amount varying with the protein intake

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[1] Wang Chi Che Frank, Margaret Hays Bertha B Kern Ruth Kaucher Mildred and Hawks Jean E. Metabolism of Undernourished Children Am J Dis Child. **32**: 63 (July) 1926 II Basal Metabolism ibid. **32**: 350 (Sept) 1926 III Urinary Nitrogen with Special Reference to Creatinine ibid. **32** 360 (Sept) 1926 IV Calcium Metabolism ibid. **35**: 856 (May) 1928 V Protein Metabolism ibid. **35** 968 (July) 1928 VI. Caloric Balance, ibid **36** 979 (Nov) 1928 VII Effect of High and Low Protein Diets on the Nitrogen and Caloric Balance of Undernourished Children, ibid. **36** 1161 (Dec.) 1929 VIII The Effect of High and Low Protein Diets on the Excretion of Creatine, Creatinine and Ammonia ibid. **38** 468 (Sept.) 1929 IX A Study of the Basal Metabolism Caloric Balance and Protein Metabolism During a Period of Gain in Weight ibid. **38** 476 (Sept) 1929

The results of this prolonged investigation of the metabolism of undernourished children, which was based on a study of eighty-three children, whose periods of stay in the hospital ranged from three to twenty-eight weeks, appear to have been largely negative in that they brought to light no striking or essential abnormality of metabolism in the undernourished child, if the latter is free from physical defects In the establishing of this point lies the chief value of the work Positive observations of practical value are that the underweight child can be made to gain in weight if sufficient attention is paid to its diet and food habits, and that the growing child requires a high protein intake

A "BITE" BETWEEN MEALS

In a government report[1] on recent economic changes in the United States, a committee under the chairmanship of Herbert Hoover while he was secretary of commerce noted that as a people we have become steadily less concerned about the primary needs—food, clothing and shelter We have long since lost all fear concerning our food supply, the report continues, and so we no longer look on food as a luxury or as a primary source of pleasure The slogan of "the full dinner pail" is obsolete During the World War the thesis that "food will win the war" was stressed everywhere, so that food fuel, measured most conveniently in terms of calories, gained a respectful consideration in every household where the conception of energy as a source of human activity could be adequately appreciated Meanwhile progress in the study of the science of nutrition introduced new conceptions into our knowledge The story of the vitamins, dietary essentials that cannot be evaluated in terms of calories, was developed It contained chapters that are dramatic in interest and almost miraculous in their implications The action of these accessory food factors has proved to be something far more important than an evanescent hypothesis in nutrition Similarly the rôle of inorganic nutrients has acquired greater importance in the eyes of dietitians, so that calcium, phosphorus, iron, iodine and other elements involved in mineral metabolism are no longer largely overlooked, as they were a generation ago, in the practical consideration of the diet One need merely read the food advertisements of the present day to learn how prominent the features other than food fuel have become in modern sales promotion Nor is this primarily quackery, it is rather the reflection of current education in nutrition

Perhaps this is a proper time at which to attempt to restore the consideration of calories to its normal place and to endeavor to secure a better perspective with regard to the essentials of a healthful regimen Recently the statement was made[2] that the present-day tendency in matters of diet is to stress the vitamins and minerals, and yet our main need for food is to secure energy, as energy is just as necessary to run the human machine as it is to run any prime motor Two features of the energy aspect have received special stress One of them is the formerly unanticipated magnitude of the food requirement during adolescence It has been pointed out[3] that the food of growing children and of youths is relatively more expensive than that for adults, because of their higher expenditure of energy in proportion to size and the greater need for building materials and vitamins, which are more costly than simple foods This writer[3] insists that, if rigid economy must be practiced, let it be as far as possible on the seasoned adult, who can best bear it, and not on developing young persons, whose right is not only to be well born but also well reared

A second feature in relation to the energy factor in nutrition deals with what has been termed "girth control" The momentary dictum of the style that calls for the "sylph-like figure" has brought calory intake prominently into the ken of those who pursue it In either case, whether in the search for adequate food for growth or in the determined effort to avoid increment in weight, the necessity of counting the calories obtrudes itself into the situation It is no longer merely a question of meal-time habits Americans are confronted with the opportunity of "in between" lunching in numerous places The sandwich shop, the tea room, the candy counter, the soda fountain, the ice cream parlor and other purveyors of food outside the routine of the usual meals beckon to the debating potential customer After all, what differences do the slight dietary digressions referred to involve? Are they really to be reckoned with seriously in terms of food fuel?

A quart of milk at 12 cents affords 33 Gm of protein and nearly 700 calories This may be taken as an item for comparison In a recent survey[2] at inland communities which may be regarded as representative of "average" American centers it was found that the conventional sandwich costing 10 cents yielded nearly 200 calories Servings of ice cream at 15 cents averaged about 200 Gm in weight, 500 calories of total energy and 7 Gm of protein The energy value per 10 cents of sundaes from drug stores was about 250 calories, or nearly 100 calories less than in the ice cream One pint of chocolate milk shake (not greatly unlike the widely advertised concoctions recommended to produce "drugless sleep") furnished from 450 to 500 calories and from 14 to 15 Gm of protein The unending variety of so-called inexpensive candy bars that are sold by the millions of packages at news and cigar stands afford, on the average, 450 calories per 10 cents The list might readily be expanded, but the essential conclusion is that the occasional "nibble" or "bite' in which the American people indulge between meals is by no means devoid of energy, particularly when reckoned as an addendum to the conventional 2,700 to 3,000 calories supplied daily by the routine three meals This is not a sermon, it is an exposition of nutritive truth

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[1] *Recent Economic Changes in the United States* Elimination of Waste Series U S Dept. of Commerce, Washington D C. 1929

[2] Benedict F G and Farr A. G The Energy and the Protein Content of Food Regularly Eaten in a College Community Bull 242 New Hampshire Agric. Expt Sta May 1929

[3] Rose Mary S Feeding the Family ed. 3, New York Macmillan Company 1929

Incidentally, the New Hampshire studies [2] that have supplied these facts of analysis further indicate that the energy value of the total food consumed daily, weekly or for any period of time may be estimated, in terms of its fuel value, with a relatively high degree of accuracy by obtaining the air-dry weight of a food mixture and multiplying it by the factor 5 This relatively simple procedure does away with the necessity for the use of complicated apparatus, it gives the physician and the dietitian a ready means of calculating the energy intake with a degree of accuracy sufficient for most purposes

WARNING PROPERTIES OF CERTAIN INFLAMMABLE HYDROCARBON GASES

Twenty-five years ago, city conveniences were the envy of the rural inhabitants Today there is little cause for envy To the farmer and villagers have come the telephone, the electric current, the radio, the central heating plant (furnace) and, quite frequently, the modern bathroom One great convenience not generally obtainable is gas for fuel in the kitchen Recently, cylinders containing certain hydrocarbons under high pressure have been made available, and these may be utilized just as is city gas for heating purposes These gaseous products have generally been rectified from natural gas and consist of such highly volatile hydrocarbons as propane, butane, pentane, hexane and heptane The applications for the use of the gases have increased enormously in a relatively short period One of the gases or a mixture of a number may be employed for cutting glass, for particularized industrial uses, and as a refrigerant This increased usage, much of which is ultimately in the home, makes more possible the occurrence of inflammable atmospheres arising from accidental leakage Unlike methyl chloride, which has been the subject of recent investigation, these hydrocarbon gases do not have marked toxic properties, nevertheless, explosive mixtures may develop

Health and safety against hazards from contamination of the atmosphere in confined spaces depend to a considerable extent on whether or not the contaminating agent possesses sense perceptive properties of an appreciable nature If distinct and easily recognized warning is given, hazards are lessened, if warning properties are inadequate, the hazards are augmented

The Bureau of Mines was requested by one manufacturer to investigate the warning properties of the highly volatile hydrocarbons in liquefied natural gas products, the problem was to ascertain whether leaks or escape of vapors could be detected in advance of dangerous concentrations The report of Patty and Yant [1] of the Bureau of Mines, now available, answers many questions The odor intensity and physiologic response produced by vapors of both the commercial and the purified gases in air were studied by exposing persons to concentrations of vapors ranging from zero, through the minimum detectable amount, to concentrations which produced a strong odor, if the last was attainable with the particular product Tests were made by both the continuous exposure method and the intermittent exposure method.

The odor and physiologic response were found to increase with the increasing number of carbon atoms in the substance (C_3H_8, C_4H_{10}, $C\ H_{12}$, C_6H_{14}, and C_7H_{16}) The odors of heptane and hexane were easily noticeable in concentrations below their lower inflammable limits Likewise, heptane and hexane vapors produced distinct symptoms, principally vertigo, after a few minutes' exposure to concentrations below their lower inflammable limits The odor of pentane was indistinct and that of butane and propane was practically absent in lower inflammable limit mixtures Also distinct warning symptoms were not produced after several minutes' exposure to hazardous vapor-air mixtures of pentane, butane and propane The investigators point out that persons whose duties entail frequent exposure to the substance in question may become more tolerant than those used as subjects for the tests, thereby requiring higher concentrations or longer exposure, or both, to cause distinct symptoms

In the absence of properties which will give warning in event of escape of the vapors, Patty and Yant recommend that a warning agent should be added to propane, butane and similar products contained under pressure which are dispensed for general use as a fuel gas in confined spaces, especially in homes It is well that the industry has had the foresight to suggest such investigations before the welfare of the public has been jeopardized, as was the case with regard to methyl chloride refrigerants The processes for adding warning agents, and their usefulness are not, however, a settled matter In the case of the liquefied natural gases, the problem appears easier than in the case of methyl chloride

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[1] Patty F A and Yant, W P Odor Intensity and Symptoms Produced by Commercial Propane Butane Pentane Hexane and Heptane Vapor Reports of Investigations number 2979 U S Bureau of Mines December 1929

Current Comment

EARLY ABORTION AND STERILITY

With the exception of those cases of sterility which are due to the absence of mature gametes, sterility and early abortion may fairly be assumed to result from the same disorders Both may be due to inherent defects in the gametes themselves, to incompatibility between them, or to an unfavorable environment surrounding the fertilized ovum The inherited and the environmental factors each received emphasis at the recent discussion of this subject before the Royal Society of Medicine in London[1] Prof Arthur Robinson was the champion of the former point of view He brought to its support the results of painstaking research on the fate of 1,643 ova shed from the ovaries of 165 ferrets More than 30 per cent of these failed to produce living offspring By making serial sections of the oviducts and the uteri, in the early stages, and sections of zygotes and of embryos in the later stages, it was possible to determine what had happened to the majority of the shed ova that had failed Some of the shed ova had not been fertilized although plenty of spermatozoa were present Robinson assumes that in these cases ova and spermatozoa were for some reason incompatible Although most of the ova had been fertilized, about 40 per cent of the zygotes had failed to give rise to living young Since multiple young are produced in these animals and since the dead zygotes are found in the same uteri with living embryos that normally will proceed to term, Robinson argues that the constitution of the dead zygote must be at fault, because its environment is not different from that of the living embryos Professor Whitehouse considers the site of implantation of the zygote and the conditions of its subsequent nutrition to be more important factors Implantation in the decidua of the lower uterine segment is, he believes, usually followed by death The decidua of the upper uterine segment depends on the integrity and normal function of the corpus luteum Diseases of this gland or malnutrition due to abnormal positions of the uterus lead to abortion Lesions are not confined to the embryo in many of these aborted ova the chorion as well is usually diseased Every form of abnormal ova and monster can be produced from normal ovaries and spermatozoa by artificial interference with the environment Moreover, when implantation occurs in so abnormal a site as the tube, 96 per cent of the embryos are abnormal The question arises as to whether a threatened abortion should receive conservative treatment since the possibility of the subsequent birth of a monster must be borne in mind Professor Whitehouse recalled two cases in which abortion was staved off successfully only to result in the birth of children with anencephalus and spina bifida, respectively In support of the view that nutrition of the embryo may play an important part in its survival, he quoted case histories of women who after several unsuccessful pregnancies had given birth to full term babies when due attention had been paid to their nutritional requirements during pregnancy Both these views deserve consideration Perhaps from the clinical point of view it is less important to determine the relative frequency of inherited or environmental defects than it is to bear in mind that either may be the cause of trouble

PREVENTABLE BLINDNESS

The prevention of blindness depends on an intelligent appreciation of its various causes and of their relative importance Unfortunately, reliable statistics as to the amount and the causation of blindness are hard to obtain On this account the painstaking research of the commission for the blind in Colorado is of permanent value True, the results do not include records of all the blind in the state, for not all the blind apply for relief, but all the blind that have come to the attention of the commission have been carefully studied, for the most part by specialists, and the causes of blindness accurately determined To the 1,053 cases in the official records have been added 150 cases from the private records of Dr Edward Jackson,[1] who now reports the investigation The commonest cause of blindness was found to be cataract (460 cases), in most cases of the senile type Opacity of the cornea accounted for 157 cases, of which forty-nine were the result of trachoma Ophthalmoscopic examination revealed lesions of the retina and choroid in 151 cases Syphilis was shown to be the cause of atrophy of the optic nerve in twenty-two cases and was probably the cause of many more of the remaining 110 cases of atrophy There were ninety-seven cases of glaucoma, causing blindness though not yet advanced to the stage of optic atrophy High myopia was certainly the cause of forty-three cases and probably of others Injury was directly responsible for loss of sight in sixty-six cases Dr Jackson believes that sight might have been preserved in the majority of these cases had adequate treatment been provided in time Physicians are called on to make early diagnosis of disease that may lead to blindness even though, at the time, the eyes themselves are little if at all affected They should also remember that some diseases that do not usually lead to blindness may occasionally do so The ophthalmologist, for his part, must be prepared to decide promptly on surgical intervention when by this means alone he may save the patient's sight

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[1] Discussion of the Causes of Early Abortion and Sterility Proc. Roy Soc Med (Section of Obst. & Gynec and Section of Comparative Med) 23 1 (Dec) 1929

[1] Jackson Edward Causes and Prevention of Blindness in Colorado, Am. J Ophth. 12:965 (Dec) 1929

TABLE 2.—*Summary of Cases of Bronchial Asthma.*

Case No.	Age and Sex.	Hist. in years.	No. and Type of Attacks.	Aerosol		Other Treatment.	Results.		Remarks.
				No. of Courses.	Days.		Immediate.	18 months follow up.	
1	12 M	3	Severe, frequent . .	3	30	Adrenalin m 1. vit. C 200 units. Tonsillectomy.	Relieved.	Only 3 mild attacks.	Improved.
2	8 M	1½	7—becoming more severe.	4	28	Tonsillectomy . .	Relieved	No attacks . .	Cured.
3	25 F	6	Becoming more severe & frequent.	4	40	Course of deep X Ray	Relieved	Occasional attacks mild—controllable.	Improved.
4	19 M	3	4—mild . .	2	20	Course of Cat. vacc. and Soamin.	Relieved	No attacks . .	Cured.
5	30 M	8	Many. frequent.	4	60	Cat. vacc. course . .	Relieved	During last 6 months attacks more frequent.	No change
6	11 M	1	8—severe . .	4	40	Tonsillectomy . .	Relieved	No attacks last 19 months.	Cured.
7	29 M	3	Severe, many . .	3	45	Adrenalin m l. Tr. for Chr. amebiasis.	Relieved	14 mild attacks in last year.	No change
8	32 F	15	Many, becoming more severe.	5	50	Adrenalin m l. early part of treatment.	Relieved	Attacks milder but persistent.	No change
9	44 M	12	Many . .	4	40	Zephrol m 2. Tr. for amebiasis.	Relieved	Attacks very mild controllable.	Improved.

TABLE 2.—*Summary of Cases of Bronchial Asthma.—Contd.*

Case No.	Age and Sex.	Hist. in years.	No. and Type of Attacks.	Aerosol		Other Treatment.	Results.		Remarks.
				No. of Courses.	Days.		Immediate.	18 months follow up.	
10	28 M	2	Many	4	48	Soamin & Anti cat. vacc.	During tr. temporary relief.	Attacks less frequent.	No change.
11	14 M	2	Many	3	45	Tonsillectomy Cat. vacc. course.	Relieved	No attacks for 16 months.	Cured.
12	20 M	6	Many, mild ..	4	60	Cat. vacc. course ..	No appreciable change.	Same frequency	No change.
13	20 F	1	6—becoming more severe.	4	48	Soamin course Deep X-Ray.	Relieved	Mild, less frequent.	Improved.
14	17 F	5	Becoming more severe & frequent.	4	60	Cat. vacc. & Soamin courses.	Relieved	3 mild attacks in 18 months.	Improved.
15	6 M	1½	Becoming more frequent.	4	48	Tonsillectomy ..	Relieved	No attacks. ..	Cured.
16	5 F	2½	Started with whooping cough more frequent.	3	42	Carbarsone course ..	Relieved	6 mild attacks in 2 years.	Improved.
17	48 M	26	Becoming more frequent last 3 years.	5	60	Acetylarsen course because of eosinophilia, vitamins and gonad hormones.	Relieved	Few mild attacks in 1 year.	Improved.

TABLE 2.—*Summary of Cases of Bronchial Asthma.—Contd.*

Case No.	Age and Sex.	Hist. in years.	No. and Type of Attacks.	Aerosol		Other Treatment.	Results.		Remarks.
				No. of Courses.	Days.		Immediate.	18 months follow up.	
18	9 M	3	Becoming more frequent.	4	40	Carbarsone course because of eosinophilia.	Relieved	3 mild attacks in 16 months.	Improved.
19	12 M	1	Severe, frequent	4	48	Anti Cat. vacc. course.	Temporarily relieved.	Still frequent but controllable.	No change.
20	34 M	19	Becoming more severe.	4	48	Adrenalin m 1. Soamin course.	Temporarily relieved.	Less severe. frequency same.	No change.
21	32 M	5	Becoming more severe.	4	48	Tr. for Chr. amebiasis and Cat. vacc. Course.	Relieved	Only 2 mild attacks.	Improved.
22	6 F	2	Severe, frequent..	3	45	Tonsillectomy ..	Relieved	Only 4 mild attacks.	Improved

lung abscess treated by medical methods available at the time ; Allen and Blackmann collected 2114 cases of lung abscess from literature in 1936 and reported a mortality of 34.4 per cent and Smith in 1948 published a series of 2155 cases taken from literature from 1936-1944 and found a mortality rate of 34.2 per cent. Penicillin therapy certainly made a change in the figures and Smith and Billingham reported a series in 1945 with combined penicillin and sulphonamide therapy, but Bryson and his co-workers first reported on penicillin aerosolisation in 1944 with encouraging results. Others have developed methods of endotracheal penicillin instillation into cavities but these methods, while being much more elaborate, hold little advantage over aerosolisation.

It has been suggested that aerosolised antibiotics give an increased incidence of hypersensitivity due to direct contact with mucous surfaces—also that the exact percentage of antibiotic reaching the abscess cavity is doubtful in each case.

In some of the chronic cases treated by me in this series, systemic treatment with antibiotics had been previously carried out extensively with little or no result. Aerosol therapy, in some cases combined with systemic therapy and in other cases without it, proved effective, in that a clinical cure was effected although radiologically the fibrosis and destruction caused remained as large irregular shadows.

Types of lung abscess treated in this series.

Primary		
	Acute	3
	Chronic	4
Secondary		
	Bronchogenic Carcinoma	1
	Bronchiectatic	1

CASE REPORTS

Case 1 :—A male, aged 37 years, gave a history of "flu" starting 20 days previously. Symptoms at the onset were, high temperature, pains in the body and a dry hacking cough. He was treated with sulfa drugs and an alkaline fever mixture. The fever came down to 99-100°, but persisted at this level, when he was treated for typhoid. Later the sputum gradually became very profuse and purulent, and he complained of pain in the left side of the chest.

Examination :—The patient looked ill and very toxic. The cough was very troublesome and sputum profuse and purulent—occasionally streaks of blood had been noticed. Dullness was present in the left midzone and base, tubular breathing and rhonchi were heard. The white cell count was 18,000 per c.mm. The roentgenogram showed a patchy shadow in the left lung.

Aerosol therapy with penicillin was given twice daily for 12 days. The temperature dropped to normal gradually in 6 days. The roentgenogram showed improvement and a second course for 10 days was given 7 days later. There was complete clinical and roentgenographic cure.

Case 2 :—A male, aged 24 years, came with a history of fever starting 29 days previously. At first, he was treated as typhoid due to the toxic state and the absence

TABLE 3.—*Summary of Cases of Lung Abscess*

No.	Age and Sex	Length of History.	AEROSOL TR.				SYSTEMIC TR.			Fever controlled.	Results.
			No. of Courses.	Dose in lacs daily.	Days	Anti-biotic used.	Dose daily.	Days	Anti-biotic used.		
1	37 M	20 days ..	2	2 2	12 10	P P	4 lacs Nil.	6 Nil.	P Nil.	6 days Afebrile.	Completely symptom free after 2nd course. Cured.
2	24 M	29 days ..	1	2	25	P	Nil.	Nil.	Nil.	10 days ..	Clinical and radiological cure.
3	57 M	9 months.	2	2 2	20 14	P & S P & S	3 lacs 1 Gm.	10 14	P S	14 days Afebrile.	Malignant pleural effusion. Died, 2 months later.
4	27 M	4½ months.	1	2	35	P	1250 mg.	6	A	8 days. ..	Complete clinical and radiological cure.
5	18 M	1½ years (Accident.)	3	2 1 2	15 15 15	P P P	Nil. 4 lacs Nil.	Nil. 8 Nil.	Nil. P Nil.	10 days .. 3 days Afebrile.	Clinical and radiological cure.
6	46 M	12 years. (Bronchiectasis) 1 year (Abscess.)	3	2 2 2	20 14 14	P P P	4 lacs 4 lacs Nil.	10 10 Nil.	P P Nil.	16 days 7 days .. Afebrile.	Abscess signs and symptoms cured. Bronchiectasis remains.
7	38 F	20 months.	2	2 1½	20 14	P P	Nil. Nil.	Nil. Nil.	Nil. Nil.	10 days. 3 days ..	Clinical cure.

TABLE 3.—*Summary of Cases of Lung Abscess—Contd.*

No.	Age and Sex	Length of History.	AEROSOL TR.				SYSTEMIC TR.			Fever controlled.	Results.
			No. of Courses.	Dose in lacs daily.	Days	Anti-biotic used.	Dose daily.	Days	Anti-biotic used.		
8	48 M	7 months.	3	2 2 2	20 14 14	P P & S P	4 lacs Nil. 1250 mg.	6 Nil. 6	P Nil. A	Temp. Lower Same Lower	Gen. condition improved. Lost sight of patient but reported, died 5 months later.
9	51 M	2 years	3	2 2 2	16 14 14	P P & S P & S	Nil. 4 Nil.	Nil. 6 Nil.	Nil. P Nil.	7 days Afebrile Afebrile.	Symptom free. Working full time. Clinically Cured.

of physical findings. Later, penicllin 4 lacs daily was given because of the presence of leucocytosis, with very little change in the clinical condition. From the twentieth day, he started coughing up copious foul-smelling muco-purulent sputum.

Examination :—The patient looked very ill and toxic. Cachexia was marked considering the shortness of the history. The right upper zone was dull on percussion and breath sounds were tubular and bronchial in nature. Rales were present. The white cell count was 21,000 per c.mm. A roentgenogram confirmed my diagnosis of lung abscess.

Aerosol therapy twice daily was given for 25 days and no systemic penicillin was used. There was roentgenographic improvement with complete freedom from all symptoms. The patient went back to work 3 months after the start of treatment and has remained well since.

Case 3 :—A male, aged 57, came with a history of 9 months of irregular temperature. (99-101°), pain in right chest and dry cough which later became productive, mucopurulent and occasionally blood-stained. Treated at first as tuberculous infiltration, artificial pneumothorax was attempted and failed, " due to adhesions". I was consulted after a copious hemoptysis and a roentgenogram showed a clear cut cavity with a fluid level in the right midzone periphery.

The patient was extremely cachectic with a white cell count of 11,600 per c.mm. Systemic penicillin had already been given (upto about 4 million units).

Aerosol therapy was given with penicillin 1 lac and dihydrostreptomycin 0.5 Gm. mixed together twice daily for 20 days. The general condition improved and the sputum diminished and the temperature came to normal in 10 days.

Cough and hemoptysis recurred after 11 days and a second course was given. but the abscess burst into the pleural cavity and on examination of the blood-stained pleural fluid, bronchogenic carcinoma cells were found. The patient died 2 months later.

Case 4 :—A male, aged 27 years, came with the history that 4½ months previously he started with temperature of 99-100° which gradually rose in the fourth month to a swinging hectic temperature of 100-104.5°. with cough, copious purulent sputum, extreme toxemia and cachexia.

At first, treated as a case of unknown fever, then sent to the hills as suspected of tuberculosis. Streptomycin 30 Gm. had been given.

A diagnosis of lung abscess was made by me on the basis of the sputum. Very few positive physical findings were present. The white cell count was 12,800 per c.mm.

One course of aerosol therapy with penicillin was given twice daily for the first 20 days and then once daily for 15 days. *i.e.*, a total of 35 days supplemented by aureomycin 250 mg., 4 hourly for first 6 days. The patient was afebrile in 8 days and there was a complete radiological and clinical cure.

Case 5 :—A male, aged 18 years, had been involved in a motor car accident 18 months previously and fractured his left second and third ribs. He had an attack of hemoptysis 3 days after the accident and later used to cough up blood-stained sputum off and on for 14 months. The sputum became profuse and mucopurulent in about 15 months. He was treated at first for pulmonary tuberculosis. Artificial pneumothorax was tried but failed to produce "adequate collapse". The fever became swinging and hectic in type with leucocytosis. Intramuscular penicillin, 4 million units, had been given with a temporary lowering of the temperature.

Examination :—The patient was looking ill and cachectic. His temperature ranged between 101.5-104° daily. The cough was troublesome and painful. Early clubbing of fingers appeared.

Chest signs—dullness in left upper and midzones with tubular harsh breath sounds and rhonchi. A roentgenogram confirmed the diagnosis of lung abscess.

Aeorsol therapy was given in 3 courses with 10 days' intervals between courses. The response was very good.

Complete clinical cure was obtained after 3 months of treatment. Radiologically, "scar tissue occupies left apex which is retracted medially".

Case 6 :—A male, aged 46, came with a history pointing to bronchiectasis—*e.g.*, cough, fetid sputum, clubbing of the fingers, of a duration of at least 2 years. A tonsillectomy had been done at the age of 29 years under local anesthesia. He had irregular symptomatic treatment only.

One year before seeing me he had started getting fever with exacerbation of cough and fetid sputum. One month prior to seeing me the temperature became higher 103-104° daily. He was treated with large doses of systemic penicillin because of a leucocytosis with little change in the clinical condition.

Examination :—He was rather emaciated and in a toxic state. The fingers definitely showing pulmonary osteoarthropathic changes. The right midzone and base were dull with moist sounds present. The white cell count was 18,200 per c.mm. A roentgenogram confirmed the diagnosis of lung abscess.

Aerosol therapy was given in 3 courses after which all signs and symptoms of abscess disappeared in 2 months. The bronchiectasis remained as seen in a bronchogram.

Case 7 :—A female, aged 38 years, came with a history of fever thought to be "flu", and an unproductive cough both of 20 months duration. After one attack of hemoptysis a roentgenogram was taken and the case diagnosed as pulmonary tuberculosis and an artificial pneumothorax was tried but failed. One course of streptomycin 30 Gm. was given and several courses of intramuscular penicillin for a persistent leucocytosis, with little effect.

Examination :—The general condition was fair with a temperature ranging from 99.8-102° daily. The cough was troublesome and the sputum purulent and copious. The right upper zone was dull to percussion with rhonchi present. The white cell count was 11,400 per c.mm. A roentgenogram confirmed the diagnosis of lung abscess.

Aerosol therapy was given with penicillin in 2 courses of 20 and 14 days with control of the temperature in 10 days during the first course and of the recurrence of temperature in 3 days of the second course.

The patient is asymptomatic and may be considered clinically cured.

Case 8 :—A male, aged 48 years, came with 7 months history, starting with pneumonia affecting both lungs. He was treated with sulpha drugs and penicillin in large doses. During convalescence his fever with cough and expectoration reappeared. The case was neglected, and the patient went back to work.

Examination :—The patient looked ill and cachectic. The signs in the right lung were dullness, bronchial breathing somewhat tubular, with moist râles present. Moderate leucocytosis and a roentgenogram confirmed the diagnosis of lung abscess.

Aerosol therapy was given in 3 courses of 20, 14 and 14 days, each with 10 day intervals. Streptomycin was added to the second course and aureomycin was given orally during the third course.

There was definite improvement in the general condition but chest signs and symptoms were not materially changed. I lost sight of the patient, and then heard reports that he had died 5 months later.

Case 9 :—A male, aged 44 years, came with 2 years history starting with fever and dry cough. A roentgenogram showed some opacity in the left apex. He was treated with artificial pneumothorax (with partial collapse) unsuccessfully.

Bouts of higher temperature and productive sputum which the patient learnt to recognise by a sensation of gurgling in the left side of the chest. Streptomycin, Gm. 40 and penicillin about 10 million units had been given at different times.

Examination :—The patient was somewhat emaciated and pale but not toxic. Clubbing of fingers was marked. The whole of the left upper and midzones showed tubular breathing and moist sounds. The leucocyte count was 21,100 per c.mm. Roentgenograms confirmed the diagnosis of lung abscess.

Aerosol therapy was given in 3 courses of 16, 14 and 14 days each, with streptomycin added in the 2nd and 3rd courses. Systemic injections of penicillin were also added to the second course. Roentgenograms showed an improvement in the condition.

The patient has made a remarkable recovery. He is completely free from all symptoms and is back to full-time work, 6 months after the start of aerosol therapy.

"........It is of interest to oneself, and possibly to others, to look for the reasons for adopting medicine as an occupation. *Parental influence is probably the most potent factor.*

—Douthwaite, A.H. : B. M. J., 2 : 431, 1951.

The British Journal of Tuberculosis (Festival Number) quotes this extract from Pliny's Natural History : "The cure for phthisis is affected by taking a wolf's liver *boiled in wine ; the brain of a sow which has been fed upon herbs ; or the flesh of a* she-ass eaten with the broth; the last, more in particular, being the one that is employed by the people of Achaia. *Smoke of dried cow-dung inhaled through reed is remarkably* good for phthisis."

—B. M. J. 2 : 438, 25, 1951.

News about medical standards in Russia was given in London recently by two doctors who have just returned from a visit to the U.S.S.R. The chairman of the delegation from the Society for Cultural Relations with the U.S.S.R., Dr. Horace Joules, said that he had been much impressed by the treatment given in the polyclinics and by the importance attached to preventive medicine. Doctors have to spend eight hours a month teaching preventive medicine to the public or to their patients in hospital. Russian doctors had been convinced by the evidence provided by British and American doctors that smoking increases the incidence of carcinoma of the lung, and without doing any research of their own into this problem they began to publicize this fact a year ago, and it is estimated that the consumption of tobacco has already fallen by 10 per cent. An intense drive is being made to eradicate tuberculosis, and all children are vaccinated with B.C.G. ; miners and industrial workers have chest radiographs taken frequently. Private medical practice does still exist in Russia, but the number of doctors working outside the polyclinics is decreasing. There is no shortage of doctors, and Dr. I. C. Gilliland said that the doctors waited for the patients rather the other way round. (Polyclinics are dispensaries resembling the out-patient departments of the hospitals, where besides the clinical examination, radiological investigations are undertaken and routine laboratory tests are also carried out. In case the patient needs indoor stay for further investigations or for treatment, they are admitted in the hospitals).

—B. M. J. 2 : 447, 1951.

MEDICAL PROGRESS

NUTRITION AND SEX GLANDS

K. Someswara Rao,* P. S. Venkatachalam* and C. Gopalan*

INTRODUCTION

It has been vaguely believed for a very long time that diet and nutrition exercise some influence on sex function. This belief, however, was not necessarily based on scientific evidence. In the last decade, increasing attempts have been made to study the inter-relationship between nutrition and sex glands.

There is considerable evidence in various species of animals that nutritional status influences sexual behaviour. Encystment and conjugation in protozoa in unfavourable nutritional conditions, sexual reproduction in preference to the asexual type during inanition in metazoa possessing both mechanisms, the metabolic re-arrangements and changes in sex glands in certain fishes during starvation, gonadal injury in birds due to lack of certain B complex factors , failure of egg hatchability in the presence of deficiency of certain nutrients, are but a few instances of the intricate, and at present ill-understood, relationship that exists between nutrition and sex function (Mason[125]).

It has long been recognised that chronic starvation in human beings causes far-reaching changes in the sexual apparatus, such as involution of sex glands, oligospermia, diminished sexual libido, *etc.*, in the male, and sterility and menstrual irregularities in the female. During the last war when food supplies were grossly curtailed, in Holland, it was reported that about 50 per cent of the women suffered from amenorrhea and many among the remainder had other menstrual disorders. The birth-rate dropped to a third of the previous normal. When food supplies again became adequate after the termination of the war, the birth-rate shot up to figures even higher than the pre-war levels (Smith[161, 162]). Similar observations were also made during the seige of Leningrad (Antonov[5]). More instances demonstrating the influence of nutrition on various aspects of sex function could be detailed, but the actual mechanisms underlying this inter-relationship still require investigation.

The influence of nutrition on sex glands, however, seems to be a mutual phenomenon. Not only does nutrition influence the sex glands, but also a disturbance of any origin involving the sex hormones can by itself bring about alterations in the metabolism of certain nutrients. It is, therefore, convenient to study the metabolism of estrogens and androgens separately and to consider how far these are related to nutrition.

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NUTRITION AND FEMALE SEX GLANDS

Inanition :—Experiments of Mulinos and Pomerantz,[132,133] and Mulinos *et al*,[134] have shown that chronic inanition leads to a state comparable to that following on hypophysectomy—a condition of 'pseudohypophy sectomy'. In this condition there is an atrophy of the sex glands. This atrophy, however, is evidently easily reversible, because the atrophic sex glands could be stimulated to activity by the administration of the respective sex hormones or the pituitary gonadotropins (Moore and Samuels[130,131] ; Marrian and Parkes[120] ; and Mulinos and Pomerantz[133]). Drill and Burill[43] have also reported that inanition as well as a deficiency of the 'B' complex vitamins, lead to a failure of ovarian function. They also successfully reversed the changes in the deficient animals with gonadotropic hormones of the pituitary. The observations of Smith and Antonov in the famine-stricken women of Holland and Leningrad, respectively, have already been mentioned. The germinal epithelium of the ovaries and testes offers considerable resistance to degenerative changes, especially during the period of active sexual life (Mason[125]). The glands can be restored to normal at an astonishingly rapid rate after refeeding is started.

Proteins :—Guilbert and Gross[71] and Pearson, Hart and Bohstedt[141] have shown that there is a cessation of ovulation in rats on diets containing less than 5 per cent protein. Macomber[118] has reported a reduction in the fertility of rats on diets of low protein content. Courrier and Raynaud[34] have observed that when wheat or gliadin constituted the main source of protein, reproduction is interfered with. The addition of casein or lysine to such a diet restored the ability to reproduce, thus indicating the specific role of certain amino acids in reproduction.

The experiments of Silberstein *et al*[158]., Zondek[173], Israel *et al*[87] and Golden and Sevringhaus[66] have clearly shown that the liver is the site of inactivation of the estrogens. Nutritional defects affecting the liver have been shown to interfere with this process of inactivation. Unna *et al*[169]; demonstrated that on a low casein diet the inactivation of estradiol by the liver was reduced ; the addition of methionine, and to a certain extent of cystine, restored the ability of the liver to inactivate estradiol. Low choline—low casein—high fat diets, which are known to produce liver cirrhosis, were also shown to cause impaired inactivation of estrogens (Gyorgy[72]). Biskind and Biskind[20] have shown that the presence of methionine, along with thiamine and riboflavin, is essential for the hepatic inactivation of estrogens. Jailer[92] claimed that the effects of inanition on the sex glands are due to the decreased protein intake, rather than to a caloric restriction.

Carbohydrates :—An excessive or diminished intake of carbohydrates exerts no deleterious effects upon the reproductive organs of either sex. However, the mechanisms involved in the effects of maternal diabetes upon fetal development and mortality are not well understood (Mason[125]).

Fats :—Quackenbush[145], Burr,[32] and Mason[128] have reported that in the absence of unsaturated fatty acids, pregnancy may terminate in resorption, prolongation of labour, excess hemorrhage and still birth.

Minerals :—Sherman and Campbell[154] found that female rats on an increased calcium intake showed a longer reproductive period, bore more young and reared a higher percentage of them. Eckles and co-workers[46] observed the following types of reproductive failures in rats fed on phosphorus deficient diets:—complete cessation of estrus sometimes following a successful pregnancy, regular estrus cycles with no normal breedings, resorption *in utero*, irregular cycles with normal breedings, *etc.* Cox and Imboden[36] concluded from an extensive study that a calcium/phosphorus ratio of 1.0, at a calcium level of 0.49 per cent, was the ideal for successful gestation. The restriction of sodium to 0.002 per cent resulted in delayed sexual maturity and disturbances in the estrus cycles (Orent-Keils *et al*[137]. Potassium restriction also showed a similar result (McCollum[128]). On low manganese diets, female rats ovulate and conceive (Orent and McCollum[136]), but produce a high proportion of nonviable or a taxic and paralysed young (Shils and McCollum,[155]). How far all these changes are mediated through sex gland dysfunction is not known.

VITAMINS

Fat Soluble Vitamins

Vitamin A :—By virtue of its function in the maintenance of the integrity of epithelial tissues, a deficiency of vitamin A may be expected to affect the sex organs which are epithelial in origin. Changes like keratinisation of the vaginal epithelium have been observed in rodents with hypovitaminosis A. It is interesting that the vaginal epithelium of rodents responds in much the same manner to either lack of vitamin A or a higher level of the estrogenic hormone. Estrus irregularities have been reported in rats (Mason and Ellison[126]) and in pigs (Mason[125]) put on vitamin A deficient diets. However, ovulation and fertilisation seem to occur normally in mild degrees of vitamin A deficiency (Evans; [49] Mason[125]).

Vitamin D :—Normal pregnancies have been reported to occur in cases of osteomalacia. Lack of vitamin D has, perhaps, no appreciable effect on reproduction in women (Bicknell and Prescott[15]). Reed *et al.* reported an occasional increase in sexual capacity and libido in both sexes and an improvement in the rhythm of the menses with large doses of vitamin D. Since highly toxic doses alone could produce these effects, vitamin D has obviously no therapeutic application for sexual disorders.

Vitamin E :—A prominent role in reproduction was assigned to vitamin E by earlier workers. Subsequent investigations have failed to produce any clear evidence that reproductive failure in man or animals is related to vitamin E deficiency. Intrauterine death and resorption of the fetus are the classical manifestations of vitamin E deficiency in the rat. The processes of ovulation, fertilisation and implantation of fertilised ova are, however, reported to be entirely normal in vitamin E deficient rats (Evans and Burr[49]) though the young are never born, resorption occurring instead. On the other hand, Bisceglie[17] found profound degeneration of the ovarian follicles. Martin and Moore[121] also reported abnormal estrus cycles and failure to render animals pregnant in chronic E deficiency states. Attempts were made to relate sterility arising from vitamin E deficiency to dysfunction of the pituitary (Barrie;[9] Underhill[168]), and to ascribe to vitamin E properties similar to those of the gonadotropic and estrogenic hormones (Mason[124]). However, it was shown by various workers that α—tocopherol acetate had no estrogenic effect on immature female mice (Bacharach and Chance[8]), or rats (Drummond *et al.*,[45]); and that it did not alter the activity of the gonads, vagina or uterus of immature hypophysectomised adult rats (Drummond[45]). Urinary excretion of the estrogens was found to be normal in vitamin E deficient rats during pregnancy until it drops shortly after resorption (Beerstrecher[13]).

Clinical evidence with regard to the usefulness of vitamin E in habitual abortion, threatened abortion and certain toxemias of pregnancy, is at present very nebulous. In contradiction to the report of Malpas[119], Bacharach[7] concluded that in women who had two or more consecutive abortions or miscarriages, it was possible to obtain full term birth with vitamin E therapy. Shute[157] *reported an increased content of the anti*-proteolytic factors in the blood serum of vitamin E deficient rats and of aborting women, presumably deficient in vitamin E. He identified the antiproteolytic factors with estrogen-like substances and attributed antiestrogenic properties to vitamin E. Cuthbertson and Drummond[37] have questioned the reliability of the above findings. Krieger[109] also failed to demonstrate the presence of Shute's antiproteolytic factor in cases of abortion, premature labour, accidental hemorrhage or normal pregnancy.

Water-Soluble Vitamins

'B'-Complex Vitamins :—A large volume of literature concerning the inter-relationship between some factors of the B-complex and certain hormonally controlled reproductive processes has accumulated in recent years. Evans and Bishop[48] reported that rats on a vitamin B free diet became anestrus. Parkes[138] and Marrian and Parkes[120] later demonstrated that this phenomenon was due to the suppression of the anterior pituitary.

It has been already mentioned that the liver is the site of inactivation of the estrogens. Biskind and Biskind[22] have demonstrated that the deficiency of the B-complex in rats inhibits the estrogen inactivation mechanism of the liver. Seagaloff and Seagaloff,[151] Singher *et al.*[160] and Shipley and Gyorgy[156] have not only confirmed the above observations but also have shown that among the B-complex vitamins, thiamine and riboflavin alone are essential for the hepatic inactivation of estrogens. Unna *et al.*[169], Gyorgy and Goldblatt[76], and Gyorgy[72] have pointed out that the 'B' complex of vitamins cannot exert this effect unless adequate protein is ensured in the diet. Drill and Pfeiffer[44] and Jailer[91] also conclude that this failure of hepatic inactivation of estrogens in the presence of deficiencies of certain B vitamins is due to the concomitant inanition and not to the vitamin deficiency per se. Biskind[19] disagreeing with the view of Drill and Pffeiffer had pointed out that if the B-complex of vitamins operated through inanition alone, it was impossible to conceive how the inactivation could be impaired in so short a period as two days. Biskind and Shelesnyak[24] observed that it was possible in the rat to induce a stage of B-complex deficiency in which the ability of the liver to inactivate estrogens was markedly impaired though the ovary was still functioning normally.

On the contrary, from a study of estrogen estimation and estrone clearance tests in pregnant women suffering from B-complex deficiency and infective hepatitis, Zondek and Brzezinski[174] concluded that vitamin 'B' was not essential for the estrogen inactivation mechanism.

Hertz and Sebrell,[83] and Hertz [81],[82] observed that an adequate amount of folic acid was necessary for the optimal oviduct response to stilbestrol in the chick and monkey. According to these workers, the hormone only served to stimulate the new tissue formation, but the latter could not be achieved unless adequate folic acid was present. These observations were also confirmed by Kline and Dorfman[103].

Fetal resorption and the birth of a weak offspring have been reported to occur in the female rodent with pantothenic acid deficiency (Nelson and Evans), riboflavin deficiency (Warkany[170]) and biotin deficiency (Mason[125]), but how far these results are mediated through hormonal mechanism is not known. Meites *et al* [129]., have adduced evidence suggesting an inter-relationship between vitamin B_{12} and the sex hormones. They showed that vitamin B_{12} could counteract the growth depressant effect of the steroid sex hormones.

Vitamin C :—Bourne[28] showed that luteal tissue is rich in vitamin C. Elden[47] reported that the vitamin C content of corpus luteum ran parallel to the progesterone content. Pillay[144] observed a decreased excretion of vitamin C at the time of ovulation in human beings. The clinical implications of these observations are not fully understood.

INFLUENCE OF ESTROGENS ON NUTRITION

Estrogens have a decided anabolic effect in protein and mineral metabolism. Severe metabolic disturbances following castration in either sex can be prevented by the adequate intake of proteins and minerals (Jungck and Heller[93]).

The favourable influence of the estrogens on calcium absorption and retention has been demonstrated in birds by various workers (Keyes and Potter[99] ; Landauer *et al*[110] ; Benoit *et al.*[14] 1941). Dallemagne *et al.*[69] and Govaerts *et al.*[38] confirmed the above results by the tracer technique. A similar effect on phosphorus metabolism has been reported by Govaerts and Dallemagne[68]. Gardner and Pfeiffer[58] also observed that the estrogens influence both bone proliferation and the regulation of calcium levels. These findings may indicate a physiological adaptation on the part of the organism to meet the increased requirements of post-pubertal and pregnant states.

A sex difference in the metabolism of fat was observed long ago. Women were reported to show a much greater susceptibility to starvation ketosis than men (Deuel and Gulick[42]). Injections of estradiol dipropionate into immature chicks resulted in a large increase in serum calcium, cholesterol, inorganic phosphorus, lipid phosphorus and protein phosphorus (Miller[130]). Estrogens have been shown to produce a rapid rise in blood and liver lipids in fowls (Lorentz *et al.*[115],[116]) and in rats (Loeb[113]). Of all the blood components, the fatty acid, cholesterol and lipid phosphorus showed phenomenal changes after estrogen administration (Heller and Thayer[79]). Fatty infiltration of the liver, which occurs to a greater extent in female rats after partial hepatectomy (Mackay and Carne[117]), is found to decrease after ovariectomy (Szego and Roberts[166]). On the other hand, Gyorgy *et al.*[77],[78], attributed a lipotropic role to the estrogens. Bird[16] has demonstrated that in male birds treated with estrogens there was, (a) a depression of metabolic rate, (b) a pronounced lipemia and (c) a markedly greater intake of food. This depressed metabolic rate in fowls allows an increased conversion of carbohydrates to fat. Estrogens thus gained commercial importance and were used for fattening market poultry (Heller and Thayer [79]).

Miller[130] observed that there was a marked fall in the potassium of the muscles of rats injected with estrogens, progesterone and testosterone. On this, he concluded that these steroid hormones had an action on electrolyte metabolism similar to that of DOCA.

NUTRITION AND MALE SEX HORMONES

Inanition :—Inanition in animals and human beings is followed by testicular atrophy, suppression of spermatogenesis and diminished libido (Anitschkoff and Sawodski[4] ; Stefko[163], Stieve[164] ; Stone[165] ; and Martino[122]). Though the germinal epithelium of the testes is resistant to a certain degree to degenerative changes, the functional impairment is marked and is probably due to a decreased output of the gonadotropic hormones of the anterior pituitary. Observations on the effect of severe inanition in human beings were made during the second world war. Klatskin, Salter and Humm[101] observed cases of gynecomastia in American prisoners of war, associated with testicular atrophy and decreased output of androgens. Similar changes following starvation were also reported by Jacobs[90]. Gopalan, *et al.*[67] observed testicular atrophy, gynecomastia and changes in the secondary sex characters in subjects suffering from the effects of chronic starvation. Gilbert and Gillman[59] using the poor South African diet of Bantus produced testicular damage in experimental rats.

Proteins :—The effects of lowered protein intake upon the reproductive organs are considered to be generally similar to those resulting from inanition. During recent years considerable attention has been paid to the possible role of arginine in reproduction. It was reported that arginine deficiency in man induced a marked reduction in the sperm count (Holt *et al.*[85]). Bryson *et al.*[31] observed that niacin deficiency resulted in the decreased inactivation of testosterone by the liver in rats. A similar impairment of liver inactivation of androgens was observed in rats on diets deficient in tryptophane. Since tryptophane is shown to be necessary for the synthesis of niacin in rats, the mechanism underlying both these observations is perhaps similar.

Maun *et al.*,[127] observed that a deficiency of phenylalanine, leucine and histidine resulted in a severe degree of testicular atrophy in the rat. The role of the essential amino acids in human reproduction is as yet not understood. In diseases like nutritional edema, liver cirrhosis, *etc.*, attributable to protein deficiency, degeneration of the testes is a phenomenon frequently reported (Davies[39], Gilbert and Gillman[59], Gopalan, *et al.*[67]).

Fats :—Mason[123], Burr[32], Quackenbush *et al.*[145] have reported that in the absence of unsaturated fatty acids the seminiferous epithelium of the testes in rats, undergoes extensive degeneration.

Minerals :—Of the minerals, manganese deficiency has been shown to produce an absence of spermatogenesis and sterility in male rats (Boyer *et al.*[29]).

Fat Soluble Vitamins

Vitamin A :—Guggesberg[70] observed hypoplasia of the testes in rats on vitamin A deficient diets. Atrophy of the germinal epithelium, which is reversible in early stages, has been reported (Mason,[123]). Hodgson *et al.*,[84] observed that bulls sufficiently deficient in vitamin A, to show blindness, lack of co-ordination, weakness, *etc.*, had cystic pituitaries, a low concentration of semen and degenerated testes ; inspite of all this they were reported to be still fertile.

Vitamin E :—Varying testicular changes have been reported in different animals on vitamin E deficient diets. No testicular changes were observed in the mouse, only reversible changes were noted in the testes of the guinea pig, rooster and hamster, while irreversible testicular degeneration was reported only in the rat (Mason[125]). Immotility and agglutination of spermatozoa have been observed in vitamin E deficient rats (Lecoq and Isidor[111]). That the interstitial tissue of vitamin E deficient animals continued to function was shown by the fact that the weights of the prostate and seminal vesicles were relatively normal. (Evans and Burr,[49] and Mason). Mason[127] suggested that testicular damage in vitamin E deficient animals was not mediated through the pituitary. Adamstone[1] showed that vitamin E can reinforce the action of testosterone in caponised male fowls.

Water Soluble Vitamins

Vitamin B complex :—Serious impairment of fertility in rats has been reported to occur in deficiencies of thiamine and riboflavin (Coward *et al.*[35]). Severe thiamine deficiency has been known to cause loss of libido though the testes may appear normal. A functional testicular failure, mediated through the anterior pituitary (Moore and Samuels[131]), may be postulated in these cases.

Like estrogens, the androgens also are inactivated in the liver. Biskind and Biskind[23],[26] have shown that inactivation of androgens by the liver is not significantly affected in B complex deficiency. They have thus postulated that certain clinical manifestations, attributable to an excess of circulating estrogens observed in B complex deficiency states, can be explained to be the result of an alteration in the estrogen/androgen ratio. However, Bryson *et al.*[31] have observed that on niacin deficient diets, the destruction of testosterone by the liver tissue of rats decreased to one-half that of the controls. According to them, thiamine deficiency also produced a slight decrease in the rate of destruction of testosterone by the liver.

Testicular damage has been reported in riboflavin, pantothenic acid and pyridoxine deficiencies in certain rodents, but the possible role of inanition in these cases has not been ruled out (Mason,[125]). Testosterone propionate was found to be less effective in stimulating the seminal vesicles of rats deficient in folic acid (Kline and Dorfman[102]), and the oviduct of chicks deficient in folic acid, nicotinic acid or riboflavin (Kline, *et al.*[104]). The diminished oviduct response to testosterone in chicks deficient in nicotinic acid and riboflavin was, however, attributed by these authors to concomitant inanition.

INFLUENCE OF ANDROGENS ON NUTRITION

The androgens, in addition to being general metabolic stimulants, help tissue protein synthesis and mineral retention. As long ago as 1891, Bogrov[27] observed a decrease in the urea excretion after injections of testicular extracts. Kochakian[106], Kochakian and Murlin[107], and Kenyon *et al.*[96] reported that injections of testosterone stimulated a retention of nitrogen in both animals as well as human beings. However, in normal men and animals, the protein retention effect was not so striking as compared to the earlier experiments on eunuchoid men and castrated animals (Kenyon *et al*). It was also observed that neither an increase in the hormone administered nor an increased nitrogen intake above certain levels favoured any greater nitrogen retention (Kenyon and Sandiford[98]; Kochakian[106]). Since this protein retention effect of testosterone does not seem to be mediated through any of the other endocrine glands (Kochakian[105], Thorn and Engel[167], Kenyon and Knowelton[95], Gaebler and Tarnowski[56]), it is believed that testosterone probably exerts a direct effect on tissue protein synthesis. Butler, *et al.*[33] found a decrease in the excretion of urea and a slight increase in the excretion of ammonia on injecting a fasting man with testosterone propionate, indicating that testosterone could also act by conserving endogenous nitrogen. Basset and co-workers[10] observed that an increase of carbohydrate in the diet considerably enhances the nitrogen retention effect of testosterone. The fact that testosterone has got a protein sparing effect has also been shown by the experiments of Farber *et al.*[50]. Male rats are found to be refractory to fatty infiltration of the liver caused by ethionine, an antagonist of methionine. Since castrated males lost their resistance to the toxic effects of ethionine, and testosterone protected both females and castrated males against this fatty liver, they believed that testosterone was responsible for this protective action which was perhaps mediated through its protein sparing effect.

Like estrogens, the androgens also have a stimulating effect on the osteoblasts (Reifenstein and Albright[147]). By virtue of this action they promote bone matrix formation and calcium retention.

CLINICAL IMPLICATIONS

Although certain clinical signs and symptoms attributable to endocrine dysfunction were frequently observed in syndromes caused by nutritional deficiencies, their association was till recently considered to be merely coincidental. From a review of the existing literature regarding the inter-relationship between nutrition and the sex glands, the pathogenesis of some of these manifestations become obvious. Recently, an understanding of this inter-relationship has even led to the treatment of some endocrine disturbances with certain nutrients, with reported successful results.

Signs attributable to diminished gonadal activity have been observed in human beings in various nutritional deficiencies. Amenorrhea, impotence, loss of libido and sterility, *etc.*, are seen in conditions of famine and war (Smith [161] Antonov [5]). A striking association between B complex deficiency signs and testicular softening and atrophy has been observed by Biskind [25]. Correction of the dietary deficiency was claimed to have relieved the signs attributable to endocrine dysfunction in both the above instances. Testicular atrophy in the males, amenorrhea, infrequent bleeding, atrophy of the breast and ovaries, *etc.*, have been reported in cirrhosis of the liver (Lloyd and Williams[112]). Oligospermia in the male and some cases of threatened abortion in the female were reported to have been relieved by the administration of vitamin E (Warren; Bacharach [8]), though Jackson and Davidson were unable to support this claim entirely.

The clinical implications of the failure of inactivation of estrogens in certain nutritional deficiencies are wide and varied. Such failure of inactivation may be expected to result in accumulation of active estrogens in the blood and tissues. Certain forms of pathologic uterine bleeding, premenstrual tension, chronic cystic mastitis (Frank[51],[52],[53] Frank, Goldberger and Speilman[54]), hypertrophy of the adrenal cortex (Korenchevsky and Dennison,[108]), cutaneous vascular dilatations leading to spider nevi and palmar erythema (Reynolds and Foster ;[148] Bean[11],[12]) and mastitis (Gardner[57]), have been regularly produced by the administration of large doses of estrogens in animals. All these signs attributable to an excess of estrogens have also been repeatedly observed by various authors in certain deficiency diseases (Biskind[18]); Biskind, Biskind and Biskind[25],[26] reported a striking correlation between excessive uterine bleeding, cystic mastitis and premenstrual tension on the one hand, and severe objective and subjective indications of B complex deficiency on the other. Both these groups of symptoms showed a dramatic improvement with B complex therapy. Peters and Footer[143] also showed that excessive uterine bleeding with a persistent acyclic estrogenic endometrium is cured by vitamin B therapy. Bean[11],[12] and Perera[142] observed the occurrence of cutaneous vascular spiders and palmar erythema in association with premenstrual tension and uterine bleeding in cases of B complex deficiency. The incidence of the post-partum subinvolution of the uterus, which appeared to be related to excess estrogens, was shown to be very much lower in a group receiving adequate B complex than in the other maintained on an average diet (L. H. and M. S. Biskind[24]). Ayre and Bauld[6] observed a thiamine deficiency (as judged by retention after a test dose) in cases with menorrhagia and cervical cancer which were associated with estrogenic changes in the cervical smear. Menorrhagia has been reported to occur in cases of pellagra by Goldberger and Sebrell.

Diets deficient in certain amino acids are known to lead finally to cirrhosis of the liver (Gyorgy and Goldblatt,[73],[74],[75]). The condition known as "malignant malnutrition" also, if persistent, leads to the development of liver cirrhosis (Gillman and Gillman[62], Waterlow[171], Davies[39]). Symptoms attributable to an excess of estrogens have been noted in cirrhosis. Menorrhagia and metrorrhagia were seen to occur in early cirrhosis (Rolleston[149], Kelly[94]). Glass, Edmondson and Soll[63],[64] reported the occurrence of increased quantities of active estrogens in male patients suffering from cirrhosis of the liver. Gynecomastia and testicular atrophy attributable to an excess of estrogens were also present in these cases. Wu[172] noted histologic changes suggestive of stimulation by estrogens in the prostates of patients with cirrhosis of the liver. Palmar erythema and spider nevi were also found in cases of cirrhosis (Selye[152]), gynecomastia and testicular atrophy in males; menstrual irregularities in females suffering from Laennec's cirrhosis were also observed by Lloyd and Williams[112]. Rather[146] observed reversible testicular atrophy in cases of hepatic cirrhosis. Improvement of these symptoms with B complex and high protein diet have been reported (Patek[139] ; Patek and Post[140]). Davies[41] has reported sex hormone upset on a widespread scale in South Africans. Primary carcinoma of the liver was found to be more common in these people. Gilbert and Gillman[59] also mentioned the development of malignant tumour in the testis of one of their experimental rats put on poor Bantu diet. In this connection the observation of Hooker and Pfeiffer[86], that estrogens produce malignant tumours in mice, is of considerable interest.

It has already been mentioned that sex hormones exert a protein and mineral retaining effect. The protein anabolic effect of estrogens is not so pronounced as that of the androgens and is therefore of relatively little practical value. With regard to the mineral metabolism, however, estrogens are known to exert a more pronounced anabolic effect than the androgens. This action of the estrogens is made use of in conditions like osteoporosis, especially the post-menopausal variety (Reifenstein and Albright[147]).

The protein anabolic effect of the androgens has been made use of in such conditions as infections, burns and fractures, *etc.*, which are characterised by excessive protein catabolism. Browne and Schenker[30] found that the administration of this hormone (testosterone) decreased the catabolic process in these conditions. Testosterone propionate is found to decrease the nitrogen excretion in cases of thyrotoxicosis (Kinsell, *et al.*[100]) pituitary hypofunction (Kenyon, *et al.*[95]), Addison's disease (Thorn and Engel[167] ; Talbot, *et al.*), and also in Cushing's syndrome according to Albright, *et al.*[3] and Albright[2]. Shelton and Mark[153] used methyl testosterone in treating the metabolic deficiencies of premature infants. The group receiving this hormone regained their expected birth weight sooner and were healthier than the control group. No deleterious side effects were observed by these authors. Testosterone was also found to be of some use in cases of uremia due to cholera (Henderson, *et al.*[80]). They believed that the beneficial effects of testosterone were due to improvement in the renal function.

A distinctly beneficial protein anabolic effect was also observed in cases of cirrhosis of the liver (Rosenak, *et al.*[150], Gabuzda[55]) and infective hepatitis (Gabuzda) treated with testosterone propionate. This hormone is also being tried in the treatment of nutritional edema of chronic starvation (Gopalan, and Venkatachalam[67]).

CONCLUSION

There are still several gaps in our knowledge regarding the interrelationship between nutrition and sex glands. This brief review of the subject here may have at least served to indicate the vast potentialities and importance of investigations on this problem.

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"........The difference between the consultant and the specialist. The latter is a man who has specialized in some narrow field. On the other hand the consultant is a man of stature who is consulted by his old students, his fellow students, and even by his teachers. He is not selected on academic attainments but arrives on his prowess as a doctor.

—H. S. Harris, H.A., My Academic Life, B. M. J. : 2 : 429-431, 1951.

A survey of the 1949 incomes of physicians in the United States has been carried out by the American Medical Association's Bureau of Medical Economic Research and the Office of Business Economics. More than 55,000 doctors took part ; the average net income from medical practice of the 30,000 doctors whose returned questionaries have already been analysed is 11,058. The average earnings of physicians are above those of lawyers. The survey shows that the highest incomes are not being earned by doctors in the large metropolitan areas,...... There appears to be great economic advantages in practising medicine in smaller cities.

—B. M. J. 2 : 467, 1951.

GENERAL ARTICLE

ESSENTIAL AMINO ACIDS IN HUMAN NUTRITION.

N. C. Datta * and Nirmal Chandra Datta †

"The most fertile field in the world in medical research today is nutrition". One of the most significant advances made in this field in recent years has been the awareness of the nutritional importance of the essential units of the protein molecule—the amino acids. Twenty five amino acids are known which go to make up all varieties of proteins present in nature. It is evident that the possible number of different proteins as they exist in nature is almost infinite. The difference between proteins are largely a matter of the number, the kind and the arrangement of such amino acids in the protein molecule.

The proteins of human diet are obtained from both animal and vegetable sources. They are digested, absorbed and utilized in the form of amino acids for the formation of tissue proteins. The amino acids are the units, the building stones from which the complex structure is built, hence their importance.

We owe to Osborne and Mendel[27] the pioneer work on the effect in the diet of various proteins viewed in the light of their content of amino acids, but much of our present knowledge concerning the essential and non-essential amino acids is mainly due to the work of Rose[31]. He first demonstrated that young white rats can maintain normal growth when the protein element of the diet was supplied by a mixture of chemically pure amino acids (amino acids known to be of general occurrence in the protein molecule). The absence of certain amino acids from the diet resulted in impaired growth, losses in weight and ultimately death. These amino acids designated as "essential" could not be synthesized by animals and had to be supplied in the diet to ensure a rate of growth considered normal.

Rose[31,32] classified amino acids into two definite groups—"essential" and "non-essential" mainly on the basis of his researches on the effect of the individual amino acid on the normal growth of young rats. Rose defined an "essential" amino acid as one which cannot be synthesized by the organism out of materials ordinarily available at a rate commensurate with the demands for normal growth. A list of "essential" and "non-essential" amino acids is given in Table I.

In the group of essential amino acids, arginine occupies a unique position, since it can be synthesized by animals but not rapidly enough to permit normal growth. It is known that rats can grow fairly well on

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TABLE 1.—*The Amino Acids Essential for the Growth of White Rats (After Rose).*

Essential	Non-essential
Lysine	Glycine
Tryptophane	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Proline
Methionine	Hydroxyproline
Valine	Citrulline
Arginine	Tyrosine
	Cystine

a diet deficient in arginine but the rate of growth is markedly improved when this amino acid is added to the diet. Arginine is, therefore, included in the list of amino acids essential for the optimum growth of rats.

There exists a certain definite relationship between certain pairs of amino acids. Thus, phenylalanine and tyrosine on one hand and methionine and cystine on the other forms two such pairs.

Phenylalanine and tyrosine.—The experiments of Rose suggest that phenylalanine is an indispensable amino acid and tyrosine is not. Under normal conditions, phenylalanine is easily converted to tyrosine whereas the reverse does not take place in the body. That tyrosine can be formed from phenylalanine was shown by feeding phenylalanine containing deuterium which resulted in a deuterium containing tyrosine, isolated from the liver protein (Moss and Schoenheimer[29]).

It can also be proved that there is a definite need of tyrosine in the body. When phenylalanine is present in subnormal amounts in the diet, the addition of tyrosine promotes growth in animals. On the other hand, if tyrosine is omitted from the diet, the amount of phenylalanine has to be increased in proportion and the additional amount represent a virtual addition of tyrosine. Besides, chemically, the two are so alike that one is tempted to treat them alike.

Methionine and cystine.—Until the discovery of methionine, it had always been assumed that cystine was an essential amino acid. It now appears from the work of Rose[41] that methionine is an indispensable amino acid, while cystine is not. Methionine can replace cystine in a diet deficient in the latter, the reverse is not true : cystine cannot replace methionine. That methionine can be converted to cystine has been shown by feeding rats with methionine containing S^{35} and isolating cystine containing the sulphur isotope from the tissue protein (hair). Thus any diet which contains methionine ensures a supply of cystine to the tissue (du Vigneaud and co-workers, 1944[40]).

Block and Bolling[11] suggest a classification of amino acids into three groups—dispensable, semidispensable and indispensable as shown in Table 2.

TABLE 2.—*Tentative Classification of Amino Acids (Block and Bolling* 1944).

Dispensable.	Semidispensable.		Indispensable.
	Group A	Group B	
Glutamic acid Aspartic acid Alanine Serine Proline Hydroxyproline	Arginine Glycine Histidine	Cystine Tyrosine	Lysine Tryptophane Phenylalanine Methionine Threonine Leucine Isoleucine Valine

Arginine is called semidispensable because it is synthesized by men but at a rate not rapid enough to allow normal sperm production. Glycine is not essential for the rats or human beings under normal conditions but is necessary for optimum growth for fowls. A group of amino acids is considered semindispensable from another point of view. They are dispensable if another amino acid closely related to it is provided in the diet in amount to cover the need of both. Cystine, for example, has no effect on growth if methionine is supplied abundantly. On a low methionine diet, however, cystine becomes the growth determining factor. (Womack and Rose,[42]).

Tyrosine bears a similar relationship to phenylalanine.

The dispensable amino acids must not be considered to be of no value. They are indispensable constituents of various essential compounds in the body. They go to make up the tissue protein in the same way as the indispensable ones, but they are interchangeable, versatile and easily procurable. If the diet is lacking in one of these, the body could synthesize them from others.

Glycine, for example, is a dispensable amino acid in so far as the growth of rats are concerned but it is indispensable when dealing with the synthesis of creatine which plays an important part in muscle physiology. It is a part of glycocholic acid of the bile. Glycine is a constituent of glutathione which has certain oxidation-reduction function in the tissue. When benzoic acid is included in the diet, glycine conjugates with it to form hippuric acid which is eliminated in the urine. This is a detoxication reaction. By means of isotope technique it has been established that this simple amino acid is utilized in the body for the bio-synthesis of complex organic compounds, such as protoporphyrin of hemoglobin, bile pigment and uric acid in man. Glycine is, however, readily obtainable from other amino acids, hence it is considered as a "dispensable" amino acid.

AMINO ACIDS INDISPENSABLE FOR MAN

The experiments of Rose dealing with essential and non-essential amino acids apply to rats. These results do not necessarily apply to other animals. In so far as man is concerned, the experiments are still in the preliminary stage. Experiments have been cautiously extended to the human race to ascertain whether the same indispensability of amino acids applies to man. The criterion has been based upon the determination of nitrogen balance.

In a normal adult, the nitrogen intake is generally equal to that excreted and the individual is said to be in nitrogen equilibrium. If, however, there is a deficiency of any particular amino acid in the diet which causes a negative nitrogen balance (*i.e.*, the nitrogen excreted is in excess of that ingested) the assumption is that the diet is inadequate to maintain the tissues of the body. The condition represents a loss of tissue protein and the amino acid in question becomes an essential dietary factor.

Albanese, Holt and associates [2,3,4,21,22] carried out nitrogen balance studies on human subjects by feeding casein hydrolysate, from which one essential amino acid was removed at a time. This was followed by a study of the effect when the missing amino acid was restored to the mixture. Their study included experimental human deficiencies of tryptophane, lysine, methionine, cystine and of arginine. When either of the first three amino acids was removed, a negative nitrogen balance was obtained. The evidence derived from 30 nitrogen balance studies on healthy adults clearly points to the need for tryptophane, lysine and methionine for nitrogen equilibrium in man. These observations represent the first convincing demonstrations of the essential nature of specific amino acids in man.

Lysine deficiency in females appeared to interfere with the menstrual cycle and some subjects are said to have experienced nausea and dizziness. Although deficiency of arginine failed to induce negative nitrogen balance, a diet lacking in arginine caused a decrease in spermatogenesis and a diminution of the motility of the spermatozoa.

Rose[33],[34] studied the same problem, using pure amino acid mixtures in the ration which he administered to human subjects. He concluded that only eight amino acids are essential to man viz., lysine, tryptophane, phenylalanine, leucine, isoleucine, threonine, methionine and valine. The removal of each one from the experimental ration induced a negative nitrogen balance, whereas the return of the missing amino acid to the diet was followed by the establishment of nitrogen equilibrium. The removal of histidine did not influence the nitrogen balance. Thus, the role of these eight amino acids, as indispensable dietary components for man, is established.

The essential nature of amino acids for the maintenance of adults may not be established by nitrogen balance experiments. A number of bodily functions may suffer in the absence of dietary amino acids which do not cause the output of nitrogen to exceed the intake. There are indications to this effect. Of particular interest is the finding by Holt and Albanese[22] that when arginine is removed from the diet, the number of spermatozoa in the seminal fluid is greatly reduced. After restoration of arginine to the diet, the content of spermatozoa returned to normal. This is interesting in view of the fact that the sperm cells of certain fish contain a large quantity of arginine (no analysis of arginine content of human spermatozoa is available). The authors interpret these findings to indicate that a temporary deficiency of arginine may result in atrophy of the spermatogenic tissue and conclude that arginine is also a human dietary essential.

Glutamic acid seems to have some special relationship to brain function. It appears to improve the condition of patients suffering from mild forms of epilepsy. Price[30] and co-workers showed that in animal experiments the addition of glutamic acid to the diet results in a higher level of mental performance. It may also have a similar effect upon mentally defective human beings. The tentative explanation offered is that glutamic acid is a co-enzyme of choline acetylase, the enzyme which catalyzes the synthesis of acetylcholine, which is liberated during nerve activity.

ROLE OF ESSENTIAL AMINO ACIDS IN THE FORMATION OF PLASMA PROTEINS

That dietary protein is effective in stimulating serum protein formation has been well established. Madden and Whipple[24] have reviewed the whole problem.

Elman[15,16] showed that intravenous injection of protein hydrolysate favoured the formation of serum proteins in dogs subjected to severe hemorrhage. Injected amino acids left the blood stream with great speed and complete retention of amino acids occurred whenever a complete mixture of amino acids was injected. With incomplete mixture of amino acids (tryptophane and cystine being omitted), only slight retention occurred and negative nitrogen balance was obtained. Even if the missing amino acids were injected 8 hours after injection of the basic mixture, nitrogen balance was not obtained.

Madden and Whipple[25] have shown that arginine deficiency does not interfere with the nitrogen equilibrium in dogs subjected to plasmaphoresis but the synthesis of new plasma protein does not take place at a satisfactory rate when arginine is absent from the diet. Recently in 1945, Madden, Whipple[26] and others have carried out extensive experiments on dogs subjected to plasmaphoresis on the role of amino acids in the regeneration of serum proteins. They have found that ten essential amino acids can cause abundant production of serum proteins and maintain positive nitrogen balance. Tryptophane deficiency causes an abrupt decline in serum protein formation.

A methionine deficient diet can cause hypoproteinemia due to limited synthesis of cystine—an amino acid essential for the formation of serum proteins. Albanese and co-workers[5] have shown that hypoproteinemia and anemia are induced in rats on a methionine and cystine deficient diet. The deficiency of plasma proteins was not produced on a cystine deficient diet in the presence of methionine.

It appears from the work of Elman that retention and utilization of a mixture of amino acids require that not only should all the amino acids be available, but all be present at the same time. The indispensable amino acids must be given as a complete mixture in approximately the proper proportion. If this is true, it is not unlikely that the unequal rate of enzymic digestion of different proteins—accompanied in consequence by an unequal rate of absorption of essential amino acids from the gastrointestinal tract, may greatly influence the effectiveness of particular proteins in the regeneration of serum proteins.

PHYSIOLOGICAL TRANSFORMATIONS OF AMINO ACIDS

The functions of essential amino acids, other than for the construction of new protoplasm, is not clear. The amino acids are highly reactive in the animal body and undergo numerous physiological transformations. Apart from the formation of tissue proteins, some of the amino acids take part in the formation of urea in the ornithine-citrulline cycle. It involves three amino-acids, ornithine, citrulline and arginine and the enzyme arginase found in the liver. A number of amino acids are incorporated in the formation of insulin. Phenylalanine presumably furnishes the nucleus for the synthesis of thyroxine and adrenaline.

The brownish black pigment—melanin present in the retina, skin and hair is produced from the amino acid tyrosine by the action of the enzyme tyrosinase. The exact mechanism by which this transformation is accomplished is not known.

By the action of intestinal bacteria, tyrosine is converted to phenol, whereas tryptophane is converted to indole. These toxic phenolic bodies are then transported to the liver where they are detoxicated by conjugation with sulphuric and finally eliminated in the urine as "ethereal sulphates".

Histidine is a most interesting amino acid and furnishes a number of problems. Histidine may be decarboxylated by the intestinal bacteria to yield histamine. The kidney and intestine contain an enzyme histidine carboxylase which can change histidine to histamine, the latter being stored very largely in the lungs. Histamine has a vasodilating action, thereby lowering the blood pressure and is also a powerful stimulant to the gastric secretion.

Histamine is destroyed by histaminase, an enzyme occurring in most tissues. A notable exception is the lungs and consequently large quantities of histamine accumulates there.

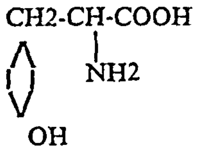
Three histidine derivatives are found in the body—thionine or ergothionine, found in the red blood corpuscles. Carnosine and anserine are found in the muscle. Their function in the body is not known. There is also some evidence to show that histidine is connected with purine metabolism.

The specific function of other essential amino acids are yet to be suggested. The phenomena of "transmethylation" recently described, is an important biological mechanism which is likely to gain more and more prominence in the future.

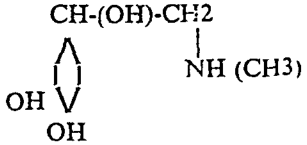
RELATIONSHIP OF AMINO ACIDS TO HORMONES

Insulin is a hormone elaborated by the islet cells of Langerhans of the pancreas. It is a protein, yielding the following amino acids on hydrolysis : cystine, tyrosine, arginine, histidine, lysine, leucine, phenylalanine, proline and glutamic acid but no tryptophane and methionine[36]. Cystine occurs in large amounts. There is some evidence that the disulphide linkage (-S—S-) which may be in the cystine portion is connected with the physiological activity.

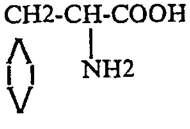
Adrenaline :—Adrenaline is produced by the medulla of the adrenal glands. Examination of its formula reveals that it is closely related to the amino acid tyrosine and the essential amino acid phenylalanine. Isotopically labelled phenylalanine when fed to animals was shown to have been converted to adrenaline.



Tyrosine

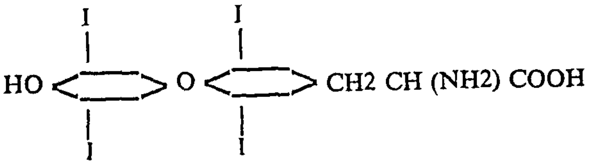


Adrenaline



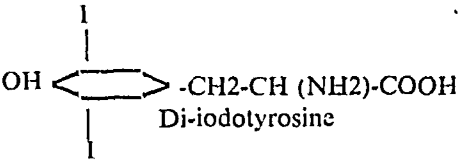
Phenylalanine

Thyroxine :—As early as 1895, Baumann made the discovery that thyroid contains the element iodine. In 1919 Kendell obtained a crystalline substance from thyroid which he called thyroxine. Harrington and Berger established its chemical formula as :—



Thyroxine

It is evident that thyroxine is closely related to tyrosine. In fact, about 70 per cent. of iodine of the thyroid gland is present as an even closer relative to tyrosine, namely di-iodotyrosine which is formed from iodine and tyrosine. Harrington and Berger[19] are of the opinion that di-iodotyrosine is the precursor of thyroxine.


Di-iodotyrosine

Thyroxine is not found as such in the thyroid gland but in the form of a protein thyroglobulin. The formation of thyroxine is thought to occur as the result of the oxidative coupling of two molecules of di-iodotyrosine with the elimination of one side chain. The thyroxine so formed, together with unchanged di-iodotyrosine and other amino acids. finally forms a molecule of thyroglobulin.

TRANSMETHYLATION

The transfer of "labile methyl group" from one compound to another is an important physiological phemonena known as "transmethylation". du Vigneaud and his co-workers[38] have demonstrated that the methyl group of methionine, CH3-S-CH2-CH-CH(NH2)—COOH can be transferred for the synthesis of other compounds in the body. The result of transmethylation is, among other things, the formation of creatine and choline, both are methylated compounds and are of utmost biological significance.

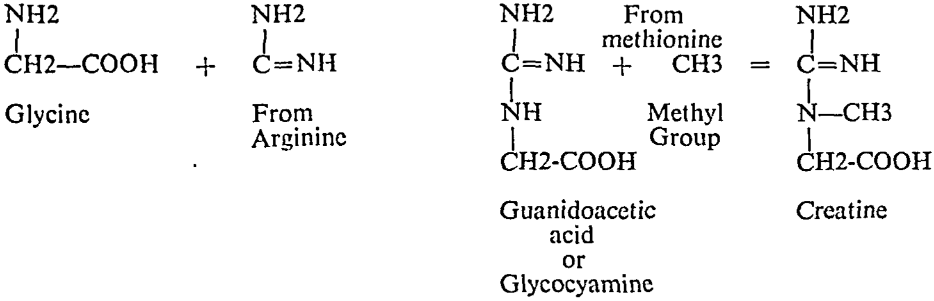
Formation of creatine :—The biological significance of creatine was for many years the subject of great controversy. The structure of the compound suggests a relationship to a number of amino acids. The clue to the identity of the possible precursor was provided by Brand and co-workers[6] who found that patients with muscular dystrophy excrete more creatine after administration of glycine. Borsook and Dubnoff[13] showed that guanidoacetic acid is methylated to creatine in surviving liver slices and that this methylation is markedly accelerated by the addition of methionine. They concluded that the methyl group of methionine is transferred to guanidoacetic acid to form creatine. Simultaneous investigation by Bloch and Schoenheimer[8] revealed that when glycine labelled with N15 is administered to normal rats, creatine with high isotope content was formed.

With the role of glycine as a precursor established and with the demonstration of the rapid methylation of guanidoacetic acid to creatine, there yet remains the problem of determining conclusively the biological sources of the various groups in the creatine molecule. Borsook and Dubnoff[14] found that kidney slices could form guanidoacetic acid from arginine and glycine. Bloch and Schoenheimer[9] showed that the administration of arginine labelled with N15 in the amidine group resulted in creatine of high isotopic concentration. By degradation studies it was shown that the amidine nitrogen of creatine is derived from arginine and the sarcosine portion from glycine[10].

The final link was provided by du Vigneaud[37],[39] when he showed that the administration to rats of methionine labelled with deuterium in the methyl group resulted in the formation of creatine with high deuterium concentration.

These studies established the biological source of each part of the creatine molecule. The origin, then of creatine, may be summarized as follows :

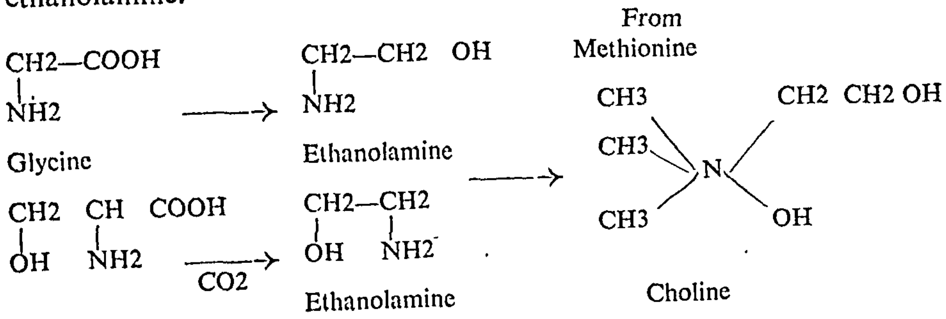
Glycine and a fraction of arginine unite to form guanidoacetic acid (glycocyamine), then the methyl group of methionine added to complete the synthesis.



$$NH_2-CH_2-COOH + NH_2-C{=}NH \;\;\; NH_2-C(=NH)-NH-CH_2\text{-}COOH + CH_3 = NH_2-C(=NH)-N(CH_3)-CH_2\text{-}COOH$$

Choline :—Choline is a component of lecithin and a dietary essential of extreme physiological significance in preventing the deposition of fat in the liver. The function of choline is in some way related to the mobilization of fatty acids in the body, since in its absence liver fat rapidly accumulates. The name "lipotropic" has been given to describe this action of choline.

The synthesis of choline is accomplished by a combination of methyl group (obtained from methionine) with ethanolamine, OH-CH2-CH2-NH2. The ethanolamine can be produced in the animal body either by reduction of glycine or perhaps by decarboxylation of the amino acid serine. It is known that anerobic bacteria decarboxylase serine to ethanolamine.



$$CH_2(NH_2)-COOH \longrightarrow CH_2(NH_2)-CH_2\,OH$$

$$CH_2(OH)\;CH(NH_2)\;COOH \xrightarrow[CO_2]{} CH_2(OH)-CH_2(NH_2)$$

Stetten[35] by feeding ethanolamine and glycine to rats on a standard diet has shown that ethanolamine is the precursor for biological synthesis of choline and that the animal had converted glycine to ethanolamine.

If methionine is added to a low choline diet, it decreases the liver fat because it has a labile methyl group to offer to the system which is lacking such groups.

ABNORMAL METABOLISM OF ESSENTIAL AMINO ACIDS

Mention may be made of certain abnormal transformations of essential amino acids in the body in certain metabolic disorders, the significance of which has not been properly understood.

During pregnancy a disturbance in the metabolism of histidine may develop with the result that a large amount of this amino acid is excreted in the urine. This occurs from the fifth week of pregnancy until a few days postpartum.

In a rare metabolic disturbance known as "cystinuria", appreciable quantities of cystine appear in the urine. A remarkable fact is that feeding cystine to such patients does not increase the output of cystine in the urine. Feeding of proteins rich in sulphur to cystinurics does increase the amount of cystine in the urine. A suggestion has been made that methionine is involved in this process.

In another rare condition known as "alcaptonuria" the urine of these patients turns black on exposure to air. This is due to oxidation of homogentisic acid, which is possibly an "intermediate compound" formed due to the faulty metabolism of either tyrosine or phenylalanine.

Another interesting anomaly of metabolism is connected with phenylalanine. Several workers have reported that certain mentally defective patients frequently excrete a considerable amount of phenylpyruvic acid in the urine. This acid is never found in the urine of normal persons. The mental condition has been given the name "phenylpyruvic oligophrenia"[23] (imbecility).

SPECIFIC DEFICIENCY SYMPTOMS

Some of the studies carried out in recent years had one of their objectives "to discover whether deficiencies of a particular amino acid produce characteristic pathological changes which could be detected by chemical or laboratory technique."

Harris, Neuberger and Sanger[20] have found that the main symptoms of lysine deficiency in rats were cessation of growth, wasting of muscular tissue and retardation of bone formation. Mitosis appears to be reduced in the testes. Serum proteins fall well below normal. The number of red blood cells and the amount of hemoglobin were slightly lower than in the control animals. The last changes seem to indicate a retarded development of the hemopoietic system.

In a study of the deficiency of sulphur containing amino acids in rats, Glynn, Himsworth and Neuberger[18] have shown that methionine deficiency in its milder degrees, produces anorexia, arrested growth and even wasting : in its severe degrees, hypoproteinemia and a special type of anemia. Cystine deficiency in diet causes massive necrosis of liver.

It is not possible at present to correlate specific deficiency symptoms with the suboptimal intake of any of the essential amino acids in man. Further progress on the effect of amino acid deficiencies should prove to be of unusual interest.

REQUIREMENT OF ESSENTIAL AMINO ACIDS FOR MAN

The usual dietaries of the great majority of the people of this country onsists predominantly of cereals and smaller quantities of vegetables and pulses. The intake of milk and animal protein is extremely low. The amount of protein and the essential amino acid available from such diets may not be sufficient for optimum nutrition of the individual. In the light of such work by Osborne, Mendel and Rose, the danger of incorporating too little protein in the diet becomes apparent. With the modern conception of "essential amino acids" it is evident that a person on a highly restricted diet might easily experience a lack of one or more of these vital building stones. If the protein or the amino acid content of the diet could be so planned as to have all the essential amino acids in requisite amount, such lack would not occur and a minimal protein diet might be the ideal one.

A study on the requirement of essential amino acids for man is a recently opened field for biochemical enquiry. It is too early to make any statement concerning the essentiality of the amino acids in human nutrition, and particularly as to the relative proportions of the various individual amino acids needed in the diet. Reference may be made of some of the work carried on in this direction.

Block and Bolling[11],[12] have analysed a great variety foodstuffs and have suggested allowances for the essential amino acids for man based on an average American diet. The daily requirement of essential amino acids for man has also been calculated from the values considered adequate for the optimum growth of rats (Rose)[31]. The figures are included in Table 3.

These figures of amino acid requirements for man appear to be too high. There were suggestions that a closer approach to actual requirements could be made on calculation based on the amino acid composition of a high quality protein. According to definition a high quality protein (*with a biological value of* 100), is one which is completely digestible and will replace nitrogen losses occurring on a nitrogen free diet without excess of nitrogen appearing in the urine. Egg protein approximates these requirements.

TABLE 3.—*Daily Requirement of Essential Amino Acids for Man*

Amino acids.	Requirement based on average American diet. gram/per day.	Calculated from data necessary for growth of rats gram/per day.
Arginine	4.7	1.2
Histidine	2.0	2.4
Lysine	5.2	6.0
Tyrosine	3.9	..
Phenylalanine	4.7	4.2
Cystine+Methionine	4.1	3.6
Threonine	3.6	3.6
Leucine	12.6	5.4
Isoleucine	3.7	3.0
Valine	3.9	4.2
Tryptophane	1.1	1.2

From an extensive compilation of data, Mitchell and Hamilton[28] showed that the nitrogen loss in urine on a nitrogen free diet was equivalent to 0.16 to 0.38 Gm. of protein per Kg. body weight per day. Thus, an intake of 0.4 Gm. of egg protein per Kg. body weight would fulfil the daily requirement of an adult. In otherwords, an adult weighing 70 Kg. would require 28 Gm. of egg protein per day for nitrogen equilibrium. From theoretical considerations, it follows that the quantities of each of the essential amino acids which are present in 28 Gm. of egg protein would be adequate for an adult.

TABLE 4.—*The Daily Requirement of Essential Amino Acids for an Adult Calculated from* 28 *Gm. of Egg Protein.*

Amino acids.	Gm/ per day.	Amino acids.	Gm/ per day.
Arginine	1.8	Cystine+Methionine	1.9
Histidine	0.5	Threonine	1.2
Lysine	1.4	Leucine	3.6
Tryptophane	0.4	Isoleucine	1.3
Phenylalanine	1.4	Valine	1.3
Tyrosine	1.0		

Albanese[1] carried out a number of nitrogen balance studies on human adults with enzymic digest of casein and calculated the daily requirement of different amino acids which would be adequate for adult nutrition. The suggested allowances including those of essential and non-essential ones are given in Table 5.

Our knowledge regarding the requirement for each of the essential amino acid for man is still incomplete. Except for a tentative suggestion, the studies on human subjects have as yet not yielded any specific information on the quantitative requirement of essential amino acids for

TABLE 5.—*Amino Acid Requirement for Adult for Nitrogen Balance with Enzymic Digest of Casein*

Amino acids.	mg. per Kg. body wt. per day.	Amino acids.	mg. per Kg. body wt. per day.
Glycine	3.1	Phenylalanine	29.4
Alanine	11.2	Tyrosine	37.5
Valine	49.4	Cystine	7.4
Leucine	60.1	Methionine..	18.5
Aspartic acid	25.6	Tryptophane	9.4
Glutamic acid	136.3	Arginine	22.6
Serine	31.2	Histidine	19.9
Threonine	22.2	Lysine	37.5

man at different stages of life and under different physiological conditions. It is to be hoped that future researches in this field will throw more light on the subject.

DETERMINATION OF AMINO ACIDS IN FOODSTUFFS

Through microbiology, significant advance has been made in our knowledge of amino acids and proteins in biology and medicine. All the amino acids except hydroxyproline have been determined by microbiological methods. Many types of biological materials have been assayed by this method since 1943 and the data have been of inestimable value in assessing nutritional quality of rations and foods.

The microbiological assay method for the determination of the amount of individual amino acid in a protein molecule is based on the fact that some of the amino acids are essential to the life of the microorganism as they are to animals. *Lactobacillus casei*, for instance, requires the presence of at least 16 different amino acids for optimum growth to occur. There is a direct relationship between the amount of each of the amino acid present in the medium (below the optimum value) and the amount of growth of the organism. Consequently, if a medium is made up which is lacking in one of the amino acids, and the substance to be analysed is added to the medium, the amount of growth will depend on the amount of the particular amino acid present in the unknown protein. Quantitative estimation of growth of *Lactobacillus casei* is made by estimation of the amount of lactic acid produced by the bacillus, either by titration or by measuring the shift of pH.

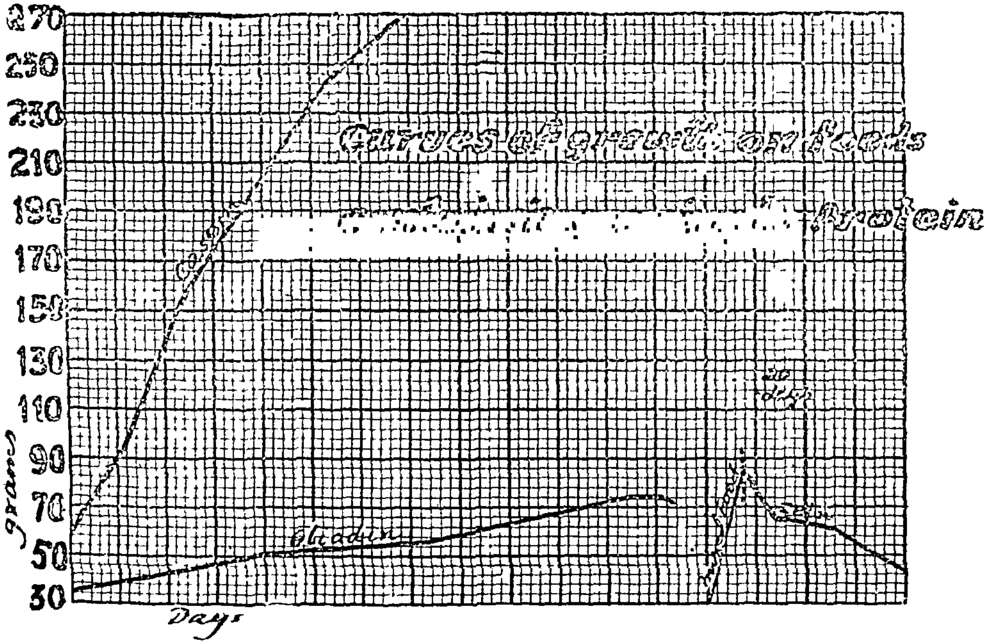
Despite any shortcomings inherent in microbiological procedure, it is becoming more and more evident that these methods have unlimited application to the determination of amino acids in all types of biological materials.

ESSENTIAL AMINO ACIDS IN SOME OF THE IMPORTANT FOODSTUFFS

The quantity of protein eaten is an important factor in nutrition. In general the protein of egg, milk, kidney and liver are the best biologically, with egg in the first place. They contain the largest percentage of amino acids.

Milk :—Milk occupies an unique place in human dietaries. It is the sole diet of infants. Block[12] states that the proteins from cow's and human milk are well balanced in the distribution of essential amino acids but human milk protein yields significantly more arginine, tryptophane and cystine plus methionine. Also, human milk appears to be richer in isoleucine. It is considered that human milk is so constituted that infants can form the maximum quantity of new tissue from the minimum amount of ingested protein.

Egg, meat and fish :—Egg, meat and fish constitute important sources of protein in our diet. They are generally classed as first class proteins with high biological value. This view has been fully supported by the distribution of essential amino acids in these proteins. Moreover, meat proteins also have a high "coefficient of digestibility" which means that the amino acids are readily split off by the digestive enzymes and are more readily available for absorption. From this point of view kidney is superior to other meats, liver next and muscle meat third. Egg protein is decidedly rich in arginine and in sulphur containing amino acids. Meat yields more lysine but less tryptophane and cystine than does

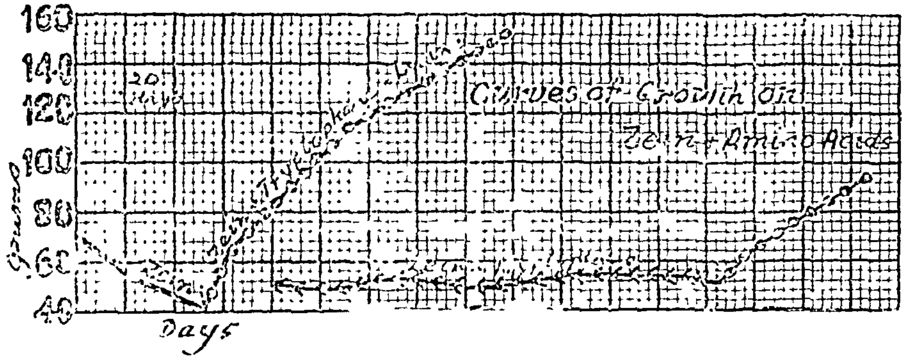


Graph. 1.—Showing typical curves of growth of rats on diets containing a single protein.

egg. There does not seem to be any marked difference between the animal and fish muscle protein, with the possible exception of lysine which may be sufficiently higher in meat protein.

Cereal, nut and legume proteins :--Cereal, nut and legume are poor sources of proteins. Cereal proteins are well known for their deficiency of lysine and for mild lack of tryptophane.

Graph 1 shows the growth curves illustrating typical experiments on the growth of rats on diets containing a single purified protein. It is evident that casein, though it contains little glycine, is suitable for growth and is a good source of protein. Gliadin of wheat is moderately low in lysine and tryptophane. With gliadin as the sole source of protein, little more than maintenance of body weight is possible. Zein of maize is markedly deficient in lysine and tryptophane, so that even maintenance of the body weight is not possible. The addition of tryptophane to the imperfect protein zein permits maintenance without growth, while further addition of lysine enables the animals to make satisfactory growth. (Graph 2.)



Graph. 2.—Showing the effect of the addition of tryptophane and lysine to zein, which is deficient in them.

Yeast, corn germ, wheat germ and soyabean yield approximately the same proportion of amino acids as do animal proteins. Of these, soyabean and food yeast have been promoted as the most promising vegetable substitutes for animal proteins. They are comparable to egg or milk proteins except for the mild deficiency of methionine.

In Table 6 is shown the distribution of amino acids in some of the common foodstuffs. (Block and Bolling)[12].

The analysis of many foodstuffs for their amino acid content is not available. However, it is apparent that mixed diet containing some animal protein like milk, fish, meat and eggs will ensure ingestion of adequate mixture of the essential amino acids. The mixture of amino acids as they occur in the protein of the foodstuffs is still to be regarded as the optimal source of the amino acids required for the synthesis of tissue protein.

TABLE 6.—*Approximate Percentage of Amino Acids in Some of the Animal and Vegetable Proteins. Calculated to 16 Per Cent Nitrogen.*

Amino acids	Yeast.	Human milk.	Cow's Milk.	Casein Gm. %	Whole egg.	Meat	Fish.	Wheat	Corn.	Soyabean.
Arginine	5.3	5.0	4.3	4.1	7.0	7.1	5.6	3.0	4.0	5.8
Histidine	3.0	2.7	2.5	2.5	2.4	2.2	1.9	1.2	2.4	2.3
Lysine	7.4	7.2	7.5	6.9	6.0	8.1	6.8	2.7	2.5	5.4
Tyrosine .. .	3.5	5.1	5.3	6.4	5.0	3.1	4.0	3.8	6.1	4.1
Tryptophane	1.5	1.0	1.6	1.5	1.6	1.2	1.3	1.0	0.6	1.5
Phenylalanine	4.6	5.9	5.7	5.2	5.6	4.5	4.5	5.7	4.5	5.3
Cystine	0.9	3.4	1.1	0.4	2.1	1.1	1.2	1.3	1.1	1.4
Methionine .. .	2.8	2.0	2.8	3.5	4.0	3.3	3.4	3.0	4.0	1.8
Threonine	5.3	4.6	4.6	3.9	4.9	4.3	4.4	3.3	3.6	4.0
Leucine	7.1	15.0	15.0	12.0	19.0	12.0	..	13.0	22.0	8.0
Isoleucine	6.0	5.2	4.4	5.0	5.3	3.4	..	4.0	3.4	4.0
Valine	4.7	5.5	5.0	7.0	4.5	3.4	..	3.4	5.0	4.6

CLINICAL USE OF AMINO ACIDS

The parenteral administration of amino acids is a recent development of great potentialities. By eliminating the process of digestion and absorption, the parenteral feeding offers a physiological method of introducing protein nourishment outside the gastrointestinal tract in a number of pathological conditions.

The most obvious reason for parenteral feeding of any kind is the inability of the patients to take food by mouth because of vomiting, obstruction of any part of the gastrointestinal tract etc. Parenteral feeding is also indicated in cases of severe diarrhoea, intestinal fistula, peritonitis and when surgery requires complete rest of the tract.

There have been a number of reports showing the beneficial effects of feeding (or in some cases injecting) certain amino acids to patients suffering from various clinical disorders.

The administration of histidine has been used, with some success, in the treatment of peptic ulcers by some physicians, while others have not found it of any value. The action of histidine, if any, is believed to be linked to the fact that histamine which can be derived from histidine by decarboxylation has a powerful action on gastric secretion.

The feeding of glycine is said to be of therapeutic value in several cases of muscular dystrophy. It is a pathological condition marked by excessive tiring of voluntary muscles and rapid decrease in their contractility. It has been already mentioned that glycine is one of the precursors of creatine, which enters into physiological activity of muscle. Much more work is, however, needed in this direction.

There are several favourable reports of clinical experience with cystine and choline in the treatment of cirrhosis of the liver (Beams[7]). There are also reports of glutamic acid being used in the treatment of epilepsy and mental retardation.

The use of pure amino acids on large scale clinical trials is at present not feasible. In general, they are difficult to prepare when obtained from natural sources, while the synthetic amino acids are too expensive. Furthermore, the synthetic amino acids are usually mixtures of equal parts of *d* and *l* forms. The use of amino acids containing considerable quantities of racemic forms for parenteral or oral feeding raises the question of the utilization and pharmacological action of unusual forms of amino acids in man.

However, it is hoped that crystalline amino acids in their natural forms will be available in plenty and at a cheaper price in the not too distant future and the ideal mixtures of pure amino acids will find extensive use as therapeutic measures in clinical trials. Until then, protein hydrolysate prepared either by acid or enzyme hydrolysis containing requisite proportions of essential amino acids can be relied on and will not act differently from a solution of purified amino acids.

The preparation of a complete protein hydrolysate is beset with many difficulties. Acid hydrolysis leads to a destruction of tryptophane. Alkaline hydrolysis, on the other hand, racemises most of the amino acids. Enzymic digestion does not give complete breakdown of the proteins to amino acids. With enzymic digestion the risk of bacterial contamination and hence of pyrogen, is very great. In the early stages, the possible dangers from the injection of protein hydrolysate were so great that this method of treatment seemed doomed to failure. However, successful intraveneous use of protein hydrolysate in animals was reported as early as 1913. The first trial of parenteral administration of protein hydrolysate on human subjects was made by Elman and Weiner[17] in 1939. Some untoward side reactions such as nausea, vomiting, temperature elevation was found to be associated with the parenteral administration of casein hydrolysate. By the use of purified hydrolysate and reducing the rate of injections, these harmful reactions have been greatly eliminated. Casein digest can now be obtained which contains all the essential amino acids and which are non-toxic to man.

Intraveneous injection of casein hydrolysate offers a physiological method of dealing with alimentation of patients in a large variety of pathological conditions. Clinical evidence so far obtained have shown that the intraveneous use of casein hydrolysate can be helpful when oral feeding is impossible, difficult or ineffective. The use of protein hydrolysate in treating patients with cirrhosis is advantageous, since the administration of amino acids as such spares the damaged liver, at the same time supplies the necessary amino acids necessary for the regeneration of serum proteins. The oral administration of the solution, whenever permissible, was found to be as effective as intraveneous injections. Clinically, the ingestion of protein nitrogen in the form of amino acids gave better results than did high protein diet by mouth.

We may expect considerable improvement in "parenteral nutrition" in the near future, as methods of producing more perfectly balanced amino acid mixture attain greater perfection. This will, it is hoped, lessen the number of obnoxious side reactions and reduce the cost, which, at present, is very high.

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CASE REPORT

GENERALISED CYSTICERCOSIS.

A CASE REPORT

A. E. de * Sa and S. N. Kothare *

Cysticercosis in man is a rare disease, and still more so the generalised form. So far only two cases have been reported in Bombay, (Dave)[3]. Recently, a case of generalised cysticercosis was met with at the K. E. M. Hospital, Bombay, which presented a variety of signs and symptoms.

Case Report.

A Christian male from Goa, aged 36 years, was admitted into the hospital for multiple swellings all over the body, attacks of giddiness and fits, and diminution of hearing of recent origin.

The first two symptoms appeared nearly two years prior to admission. The swellings had started on the flexor surface of the body and had spread gradually to involve the whole body surface. The attacks of giddiness came off and on and the "fits" were preceded by a vague aura of flashes before the eyes.

He was given to smoking and drinking alcoholic drinks in moderation. His diet was mixed and included, at times, well cooked pork. He gave a history of having passed a tape-worm four months prior to admission. He had not suffered from any venereal disease. He had undergone an abdominal operation eight years previously, the details of which he could not furnish. He also had had a fall from a bicycle nearly seventeen years previously which had left him unconscious for some time and had been followed by pain in the lumbar region of the spine.

Physical Examination :—

He was a well built, muscular man. The muscles of the calf and back were noticeably hypertrophied. Smooth globular swellings were present all over the body; the scalp alone was spared. There was one cystic swelling on the mucous surface of the lower lip. The nodules varied in size from 0.5 cm. to nearly 2.0 cm. in diameter. Some of them were situated in the subcutaneous tissue and others were deeply embedded in the muscles of the extremities and back. The consistency varied from firm to hard.

Examination of the central nervous system showed evidence of ideational retardation and the speech was staccato, deliberate and slow. There was a supranuclear type of facial paralysis on the right side. There was generalised diminution of muscular power in the upper and lower extremities and the trunk. While under observation in the hospital, the patient developed fits and twitchings of the right side of the face and the upper limbs, which showed alternate flexion and extension. On one occasion, he had as many as five fits in two hours. Apart from these, there were no other abnormalities in the central nervous system. All other systems were normal. His blood pressure was 104/50 mm. of Hg.

The following laboratory investigations were carried out :—

(1) Blood Count	—Total number of erythrocytes	—5,360,000/c.mm.
	Total number of leucocytes ..	7,700/c.mm.
	Hemoglobin	.. 17.7/Gm.

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* Hon. Surgeon, K. E. M. Hospital and Pathology Department, G. S. Medical College, Bombay 12.

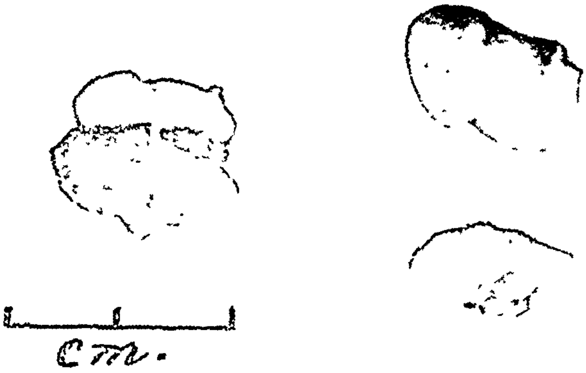

Fig. 1.—Photograph of the excised cysts (*Cysticercus cellulosae*).

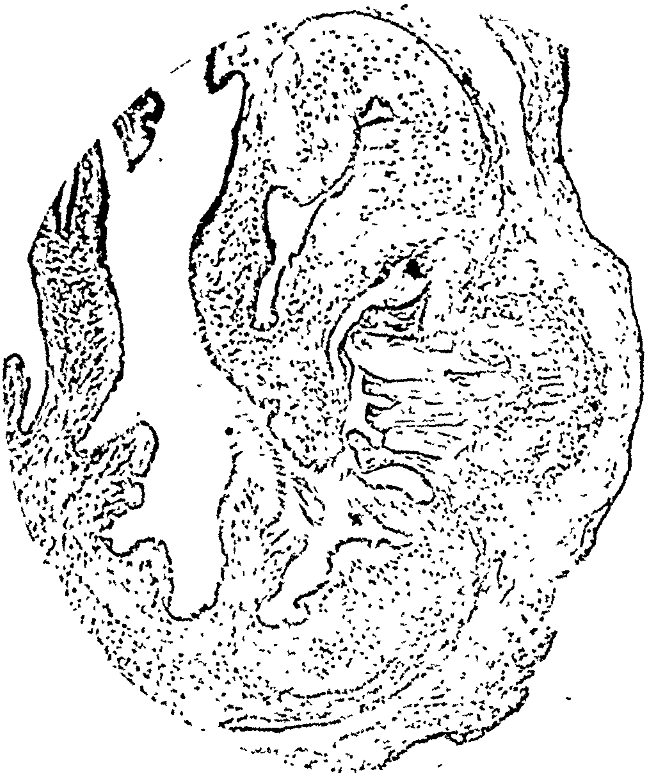

Fig. 2.—Photomicrograph of the *Cysticercus cellulosae*. H. & E. x 120.

Polymorphonuclear neutrophil cells	46 per cent.
Polymorphonuclear eosinophil cells	9 per cent.
Lymphocytes	45 per cent.

(2) Examination of the feces did not show any ova or cysts.
(3) Routine examination of urine was normal.
(4) The Kahn flocculation test on blood serum was positive.
(5) Examination of the cerebrospinal fluid :—

The pressure of the fluid was 140 mm. of water. It was clear and contained 41 cells per c.mm.; 64 per cent of these cells were lymphocytes, 33 per cent polymorphonuclear neutrophils and 3 per cent mesothelial cells. The protein content was 80 mg. per cent with relative increase of globulins (Pandy's test); the sugar content was normal and the chlorides were 650 mg. per cent. No microorganisms were detected either on smear or cultural examination. The Wassermann test with the cerebrospinal fluid was positive.

Roentgenological Examination :—

(1) A plain Roentgenogram of the skull and the lumbar spine did not reveal any abnormality.
(2) Fluoroscopic examination of the chest and the rest of the body for evidence of calcification was non-contributory.
(3) Pneumo-encephalography with a 60 cc. airfill showed a normal sized and undeformed ventricular system.

Other Investigations :—

(1) Fundoscopic examination revealed normal findings except for a slight tortuosity of the retinal vessels.
(2) Perimetry showed a generalised contraction of the visual fields on both sides.
(3) The Electro-encephalogram did not show any evidence of a space occupying lesion.
(4) The Electro-cardiogram was normal.

Clinically, it was diagnosed as a case of multiple neurofibromatosis or generalised cysticercosis. One of the nodules from the forearm excised for histologic examination showed the characteristic structure of *Cysticercus cellulosae.*

Subsequently several nodules from various sites of the body were excised for detailed study.

The nodules were either oval or ovoid in shape. Most of them were about 1.5 cm. x 0.5 c.m in size, firm to feel and the surface was smooth greyish white, and translucent in appearance (Fig. 1.). A few, on cutting showed a smooth inner lining except over a minute area. This area was about 1.0 mm. in diameter, firm to feel and white in colour,—the "Milk Spot"—The cysts contained a small quantity of opalescent, milky fluid. Microscopic examination showed the cyst wall to be composed of well formed fibrous tissue infiltrated with chronic inflammatory cells amongst which a fair number of eosinophils could be made out. The section passing through the "milk spot" showed the convoluted germinal layer of the larva, the sucker pads and the hooklets. (Fig. 2.).

COMMENT

Cysticercus cellulosae is the larval stage of the tape-worm, *Taenia solium.* In the life cycle of this worm, the pig and man play the role of intermediate and definitive host, respectively. Occasionally, the latter also becomes the intermediate host. How exactly it happens is still unknown. However, several views have been expressed to explain this phenomenon. It is believed that man may get infected by ingesting food and water contaminated with the ova ; or an individual harbouring this parasite may convey the ova to his mouth with soiled fingers ; or the gravid segments may be regurgitated into the stomach and get digested, thus liberating the embryo (Faust)[4]. The embryo enters the circulation and is likely to be deposited in any part of the body, giving rise to a cysticercus. The various parts of the body affected, in order of frequency, are the subcutaneous tissue, brain, orbit, voluntary muscles, heart, liver, lungs, and peritoneum. Symptoms, if and when present, depend upon the number and location of the cysticerci. Strangely enough the symptoms, particularly of the cerebral type, appear after the death of the larva which evokes a granulomatous reaction in the surrounding brain tissue (Anderson)[1]. The cysts are usually round and vary in size from 2 to 5 mm. in diameter. When alive the cysts are translucent and glistening ; but become dense and opaque after the death of the larva. In due course calcium is deposited in the cysts and the areas are well seen in roentgenograms.

The period of generalisation of the disease is often associated with a wide variety of symptoms and among the diverse diagnoses made at this stage of the malady are malaria, allergy and pyrexia of unknown origin. The symptomatology depends upon the location of the cysts. When situated in the subcutaneous tissue, they are easily palpable as small nodules ; the "professional wrestler" type of physique has been described in cases where the cysts were widely distributed in the muscles of the trunk and extremities. McGil[6] has recorded two cases in which the localised collection of cysts in the muscles of the calf produced an appearance closely simulating a myopathy of the pseudohypertrophic type. Depending upon the anatomical site of the cysts in the central nervous system a wide range of neurological symtoms is known to occur. Frank epileptic fits have been described by MacArthur[5]. In a study of twenty-two cases of epilepsy in British soldiers returning from India, he found that in ten of these the malady was brought on by cysticercosis of the brain. Subramaniam[8] has described a case of generalised cysticercosis in which "fugue" was a prominent symptom. One of McGill's cases also had diabetes insipidus which could conceivably have been due to a cyst in the region of the hypothalamus. Diabetes mellitus may result from a cyst in the floor of the 4th ventricle of the brain as in Osler's case (Christian)[2]. The cerebro-spinal fluid pressure is often higher than normal in cases showing cerebral manifestations. The raised intracranial tension has been known to cause papilledema and even blindness, and a timely decompression may be called for in order to save the patient's sight. In the case reported here the fluid pressure was on the high side of normal.

Diagnosis depends upon the proper elucidation of the history with special reference to the diet, roentgenography, preferably, of the whole body and biopsy examination of the nodules. Absence of ova in the feces is a common finding and autopsies are conspicuous by their failure to reveal the adult worm in the intestine. While blood eosinophilia has been considered to be of little diagnostic value, the eosinophilic cell count of 9 per cent in this case was a useful pointer.

Treatment, so far, has been essentially symptomatic and palliative. It is an ironic sidelight on the disease that symptoms are absent while the larvae are alive but begin to appear with the death of the cysts or while they are in the process of dying. On a theoretical basis the best treatment would be that which would keep the larvae alive. McRobert[7] has described a case of generalised cysticercosis which appeared to respond to treatment with antimonials (Fouadin and Tartar Emetic), though the initial injections caused a succession of epileptic fits, presumably from a specific action of the antimony on the cysts.

SUMMARY

A case of generalised cysticercosis is described. The symptomatology diagnosis and treatment are discussed.

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Do you know that ?........

In life the volume of a normal man's heart is about 700 cc.

Its weight averages 289 grammes.

The average volume of the heart muscle is about 280 cc.

The volume of blood inside the heart is 420 cc. or about twice the stroke output of the two ventricles.

—Lancet, Leading Articles, 2 : 671, 1951.

CASE REPORT

MALIGNANT HYPERTENSION

REPORT OF A CASE

S. Bera*

CASE REPORT

On the morning of the 20th January 1951, a male aged 38 years walked a distance of three miles for medical consultation. He was a strongly built farmer and looked healthy. His chief complaint was a throbbing headache over the temporal and occipital region and extreme dimness of vision. He could not identify a person at a distance of three feet. He gave a history of a severe throbbing headache off and on for the last five years which compelled him, on several occasions, to lie in bed for several days. It was accompanied sometimes by hiccough and vomiting. When the acute attacks of such headaches subsided, he used to resume the usual work of a farmer. In a similar attack two weeks prior to my seeing him, he developed an acute diminution of vision even though his headache had been relieved by some analgesics.

On examination I found the following : A pulse rate of 72 per minute, bounding and of high tension. The brachial artery felt cord-like and tortuous, the radial artery could hardly be compressed. Both the heart sounds were very loud, the apex beat was heaving in character and in normal position. The lung fields were clear. The liver was tender, palpable one finger's breadth below the costal margin. The spleen was not palpable. The blood pressure was above 250 mm./Hg. systolic and 150 mm., diastolic. The urine contained albumin.

The diagnosis was obviously malignant hypertension with albuminuric retinitis.

The treatment advised by me was complete rest in bed, Ralfen (B. C. P. W.) 15 minims three times a day, phenobarbitone ½ gr. three times a day and a sedative mixture containing magnesium sulphate.

The next day the patient's condition became worse, his headache increased considerably and he was restless. His blood pressure was the same as before. I did a venesection and withdrew more than 16 oz. of blood. He was given 50 cc. of 50 per cent glucose solution intravenously, 6 oz. of 25 per cent. magnesium sulphate solution per rectum every 6 hours and 3 gr. of phenobarbitone intramuscularly. With this treatment he had a temporary decrease in the intensity of the headache. Aspirin (10 gr.) and phenobarbitone (3 gr.) which were given six hours later caused him temporary relief. All the previous treatment was continued for the next 24 hours. A lumbar puncture, which I thought would help, could not be done.

On the next day, even though the patient was conscious with the same blood pressure, he had become completely blind. A further venesection of 16 oz. was done.

Two days later he became unconscious with typical signs of coma but the systolic blood pressure had decreased to 180 mm. systolic and 130 mm. diastolic.

On the next day his blood pressure rose again. He remained in this stage for a period of 48 hours and gradually became worse and died 9 days after my first examination.

COMMENTS

It is interesting to note, that a patient with such high blood pressure and symptoms of four or five years duration should continue to do a normal farmer's work and die, not of the usual complications like apoplexy but in a coma.

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* Baishnabchah, P. O., Balughat, via Midnapur District.

BOOK REVIEWS.

Recent Trends in Penicillin Therapy.

By the Medical Division, Infa Limited. pp. 77 with 5 charts. Published by Infa Limited, P. O. Box 1041, Bombay 1.

This booklet is written by a doctor who was a Major in the I.M.S., for the information of physicians and venereologists in this country. It is a review of the work published on penicillin in the last few years. It contains information on the various salts of penicillin, all very well arranged. Most of the references which are given are more than a year old, some of them as many as three years, in a fast-moving field of antibiotics. For a practitioner who is abreast of recent literature there is very little new in this book. However, it might be of some use to the general practitioners of smaller places in this country.

J. C. PATEL.

Auto-suggestion—How to Master it

By J. Louis Orten, Publishers :—D. B. Taraporevala Sons and Co., Ltd., Bombay First Edition, 14 Chapters and 153 pages. Price Rs. 3-12-0.

This small book, from a man of international reputation, contains numerous quotations from psychologists and other eminent men. It describes the technique of auto-suggestion in detail and in the last chapters gives common sense advice in a paternal manner. The presentation of the material is lucid and the author has avoided all technical psychological terminology, probably because the book is meant for lay intelligent people, not necessarily conversant with the subject of psychology. The author's dislike for psycho-analysis is very conspicuous and because of this the book is not likely to be very much appreciated by psychoanalytically minded psychologists and psychiatrists. Still it can be read with interest by many, even if one disagrees with the author on many points, as it is interesting to know how he explains the value of auto-suggestion as a treatment. Another conspicuous weakness of the book is the lack of statistical data, showing in what percentage of patients and in what type of illness was auto-suggestion useful and to what extent.

N. S. VAHIA.

It was his first day, apparently, in gynaec extern and life was real, life was earnest ...... "Do you ever laugh at all," he asked the patient complaining of stress incontinence "when you pass water ?"

—"This Busy World and I....". Medical World, 74 : 697, 1951.

NEWS

CONFERENCE OF THE ASSOCIATION OF PEDIATRICIANS OF INDIA

A Conference of the Association of Pediatricians of India will be held at Hyderabad—Deccan, on the 2nd and 3rd of March, 1952, at the time of the Conference of the Association of Physicians of India and Association of Cardiologists of India.

This is open to Members of the Association and all those interested in Pediatrics. Those who desire to read papers at this Conference should communicate with the Secretary of the Association of Pediatricians of India, Back-Bay View, New Queen's Road, Bombay 4. not later than the 22nd of January, and submit the title and summary of their paper.

Those who desire accommodation at Hyderabad, are requested to get in touch with Dr. Pargaonkar, Opp. Sultan Bazars Hospital, Hyderabad—Deccan.

ALL INDIA MEDICAL CONFERENCE

To,

Members of the Medical Profession in India.

Dear Doctor,

The Reception Committee of the twenty-eighth All India Medical Conference cordially invites all qualified medical men to attend the Conference at Ahmedabad on the 17th, 18th, and 19th, February 1952. The programme and other arrangements are as under :—

1. Working Committee meeting of I. M. A., 13th, and 14th, Feb. 1952.
2. Central Council meeting of I. M. A., 15th, and 16th, Feb. 1952.
3. All India Conference, 17th, 18th, and 19th, Feb. 1952.

Reception arrangements and Railway connections :—

There will be a reception camp at the Ahmedabad Station and volunteers will remain present both at metre-gauge and broad-gauge platforms for all trains. For members from Bombay and further South, Janata Express and Gujarat Mail leaving Bombay at 19-30 and 20-20 hours are convenient trains. For members from Bengal, U. P., Bihar, Punjab *etc.*, Delhi Mail ; metre gauge is very convenient, leaving Delhi at 21-30 hours. For Central India and C.P., Tapti Valley Railway leaving Bhusaval at about 23-0 hours is convenient. This train connects Saurashtra Express at Surat at about 13-30 P. M. Timely intimation must be sent for your reservations by these trains. Railway authorities have granted concessions for all classes on production of concession certificates from the organising Secretary of the Conference.

Boarding and Lodging

There will be a general camp in the premises of Sheth C. N. Vidyalaya, Ellis-Bridge, Ahmedabad, where all delegates and visitors will be accommodated with separate arrangements for ladies. There will be a camp kitchen in the same compound where all catering arrangements will be made on usual tickets. There are no good hotels in the city, hence all guests will be accommodated in the camp. Please, therefore, supply the following information to the Reception Committee immediately :—(1) Train, time and date of your arrival. (2) Train, time and date of your departure. (3) Whether you are vegetarian or non-vegetarian. (4) Whether you will stay in camp. (5) By which train and class you wish to travel back.

For any other information I am always at your service. Please get your concession certificate immediately. Thanks.

Yours faithfully,
(Sd.) P. P. TRIVEDI.

ASSOCIATION OF PHYSICIANS OF INDIA

ANNUAL CONFERENCE

The Annual Conference of the Association of Physicians of India will be held at Hyderabad (Dn.) on the 2nd, 3rd and 4th March 1952 along with the Annual Meeting of the Pediatricians and the Cardiologists.

Symposia on Infantile Cirrhosis of Liver, Rickets, Tuberculous Meningitis, Dysenteries in India, Congenital Heart Diseases have been arranged at these joint meetings. There will be, besides, other scientific communications.

For taking part in the deliberations of this Conference and for hotel accommodation at Hyderabad, I would like you to write to Dr. U. R. Pargaonkar (Opp. Sultan Bazars Hospital, Hyderabad-Dn.) who will arrange for your stay and transport. Daily charges will vary from Rs. 20 to Rs. 25. For further information please write to the Hon. Secretary, Association of Physicians of India, Back Bay View, New Queen's Rd., Bombay 4.

As a Matter of Fact :—

There are 9 billion ganglion cells in the cerebral cortex and 12 billion cells in the cells in the brain, altogether. The possible number of connections of two neuront in the human brain has been estimated as being 102,783,000. While an electric currens in a wire travels, 11,160,000 miles a minute, the nerve impulses are conveyed over the axons with a speed of not more than 4½ miles per minutes.

It has been estimated that about 10,000,000 red blood cells are destroyed (and replaced) per second in an adult. The diameter of an erythrocyte is 0.007 mm. An adult is about 250,000 times taller in size than the diameter of an erythrocyte is long. A normal speciment of semen will contain a volume of 2 to 5 cc. and a count of 75 to 100 million spermatozoa per cc.

The adult has a total of 120,000 hairs on the average scalp ; blond individuals have an average of 150,000 hairs and red haired individuals have 90,000.

In a new born male infant there are 270 separate bony units, in a 14 year old boy 350 and in an adult man, 40 years of age, 206.

Seventy per cent of the weight of the human body is water ; 50 per cent is intracellular water and 20 per cent extracellular water. 170 litres of water are filtered from the blood plasma through the kidneys in a 24 hour period.

The average American adult consumes once every 50 days his own weight in food ; a healthy child does so in about 10 days, while an old man does it only once in 65 days. In addition an adult breathes approximately one fifth of his own mass in air within 24 hours.

—Quoted from Clinical Medicine, n Medical World, 74 : 625, 1951.

Virus Multiplies 200-fold in Half Hour :—

One reason polio and other virus diseases spread so fast was indicated by Prof. Frank W. Putnam, University of Chicago biochemist, recently, when he told a symposium of the American Chemical Society that less than a half hour after a single virus particle invades a living cell, from 200 to 300 identical particles emerge simultaneously —destroying the cell.

Prof. Putnam, who described recent virus reproduction studies made with the aid of radioactive tracers, said that apparently the invading particle itself also is destroyed in the process.

—Quoted from Medical World, 74 : 695, 1951.

CURRENT MEDICAL LITERATURE

SURGERY

VACCINE THERAPY OF APPENDICITIS, CHOLECYSTITIS AND CHOLELITHIASIS, Kiemer, G. Harefuah: Journal of the Medical Association of Israel **40** : 1-4, 1951.

The author who suffered from all three conditions and suspected *B. coli* as an etiological factor obtained a remarkable cure by the use of an Enterovaccin which contains in addition to 5 milliards of *B. eberti* and 2 milliards of *B. paratyphosus A and B*, also contained 3 milliards of *B. coli* of various strains per pill. The author also had made an anti-coli vaccine prepared in the form of pills covered with a layer of keratin. Between 1924 and 1949 the author has treated 85 cases of appendicitis and 415 of gall-bladder disease.

The cases of appendicitis were divided into three groups. The first consisted of 36 cases of acute or sub-acute appendicitis which for some reason or the other were not operated upon during the first two days ; the second consisted of 48 cases of chronic inflammation and the third consisted of one case of acute appendicitis where the treatment was begun seven hours after the onset of the first attack. All theses cases were treated with the anti-coli vaccine. Of the first group, 30 recovered completely, of the second, 33 improved remarkably of which 16 showed a really lasting cure in a follow-up of over 5-15 years, while the remaining 17, though free from complaints for 2-5 years after this period, did have some symptoms though very slight. The acute case which happened to be that of the author's wife made a complete recovery and there was complete freedom from symptoms since then (1 year and 10 months).

In gall bladder disease the author has found that vaccine therapy has given a positive result in 77 per cent of cases, the explanation for the remaining 23 per cent being that the stones were either too large or too many.

The daily dose advocated is from 2 to 10 pills a day, according to the case, given for a course of at least 56 pills. According to the gravity of the condition the author has used upto 5 courses of the anti-coli vaccine and 3 courses of the Enterovaccin.

EUSTACE J. DE SOUZA.

INTRODUCTION OF BLOOD INTO THE PERITONEAL CAVITY, Mengert, W. F., Cobb, S. W. and Brown. W. W. : J. A. M. A. **147** : 34-37, 1951.

The authors carried out studies to correlate the quantity of free blood in the peritoneal cavity with the resulting symptoms, by introducing blood and other materials at varying rates in human beings.

The subjects were 16 women (twelve puerperal) about to undergo laparotomy and the protocols of the other patients with accidental and massive intra-abdominal hemorrage were included.

Injections were made under local anesthesia through a 16 gauge needle. Generally the blood was withdrawn from the patients antecubital vein. The rate of injection varied with each patient, and appeared to be a factor in the causation of various symptoms. White blood cell counts were made before injection, a few hours after injection, and on the following day.

The injection of less than 300 cc. elicited complaints of fullness in the lower abdomen and the desire to pass gas or belch. Some patients complained of uterine cramping or said the after pains were intensified. With 300-500 cc. of blood severe pain resulted which gradually disappeared after 15 to 30 minutes. The pain and discomfort were noted by even those who were unaware that any fluids had been injected, and symptoms could be evoked with succeeding injections of decreasing amounts of fluid. The pain invariably disappeared after conclusion of the injections. Tenderness to deep palpation was increased temporarily but disappeared the following morning even in those who at operation were found to have 500 cc. of bloody abdominal fluid. Five of the 16 had received injections of materials other than whole blood. Saline in one produced pain after 200 cc. but most was found to be absorbed at operation (24 hours). Plasma in two was not absorbed so rapidly but some peritoneal reaction was exhibited. Two patients received washed red blood cells suspended in Ringer's solution, but it appeared that the presence of the erythrocytes delayed the absorption of the fluids.

The pain appeared to be proportional to the amount injected rather than dependent upon the composition of the injected material. Capps and Coleman suggest that localized pain results from either pressure upon, or stretching of, the nerve endings by direct irritation of the nerve endings. About four-fifths of the blood injected remained liquid.

The clinical application of the work gave the authors to believe that in patients suspected of intra-abdominal hemorrhage, continuance of the complaint of fullness and pain indicates continuing or repeated hemorrhage.

EUSTACE J. DE SOUZA.

THE BLEEDING PEPTIC ULCER. Willcox, A.: The Clinical Journal, 80 : 253-255. 1951.

The author stresses the importance of this all too common a catastrophe and reviews the published analyses of a number of physicians and surgeons from which he bases his conclusions regarding the natural history of the condition, the risks involved and the appropriate management of the individual case. There has been an interesting fluctuation in the death rate from 5 per cent at the beginning of the century to 20 per cent in 1925 till 1935 when it began to fall again when it is about10 per cent but shows a tendency to rise again.

The type of ulcer is important. In about a third of the cases nothing abnormal is detected in the stomach or duodenum at barium meal, though in a fair proportion, acute gastric ulcers are seen at gastroscopy if it is done about the tenth day. These cases often give no history of dyspepsia. The prognosis is good whatever the age at which it occurs. The death rate from a bleeding chronic gastric ulcer is higher than that from the duodenal ulcer. The death rate rises sharply in cases over 50 years. Though it is usually held that past hemorrhages make matters worse, Needham and McConachie were not able to confirm this. Recurrent hemorrhage is particularly dangerous over the age of 50 years. Pain usually disappears with hemorrhage, and coronary thrombosis is to be feared when there is a severe loss of blood.

The essentials of treatment are to allay anxiety, and to correct shock, anemia and malnutrition, and in certain cases to seal the bleeding point. The most reliable signs are a rising or persistently fast pulse rate. The object of transfusion should be to keep the hemoglobin at such a level as to support a recurrent hemorrhage. Iron should be given when frank melena has stopped and ascorbic acid is also advisable. Partial gastrectomy is the most successful operation and those cases should be selected where any feature indicating a serious prognosis make surgery a prime consideration.

EUSTACE J. DE SOUZA.

MODERN TREATMENT OF PEPTIC ULCER, Glandon Williams, A. : The Medical Press **226** : 387-389, 1951.

The author points out that while closure of the perforation has been a fundamental principal many surgeons now advocate the non-operative treatment of perforated peptic ulcers.

While the promptness with which the diagnosis is made materially affects the prognosis, it must also be remembered that the age of the patient and the site of the perforation are important considerations affecting the mortality.

The immediate treatment is directed towards relieving shock. While morphia is withheld till the diagnosis is confirmed by a surgeon it may be given after the diagnosis is definitely made, if the patient is to be saved the discomforts of a long journey to hospital. Gastric suction should be used if there is to be any period of waiting.

While it is difficult to give any hard and fast rule for the selection of cases for the non-operative line of treatment, it is generally agreed that the treatment should be carried out in hospital, an initial dose of morphia should be given intravenously or intramuscularly and the stomach should be emptied with a large stomach tube. A Ryle's tube is then passed and attached to a continuous suction apparatus. Fluids are withheld by mouth and adequate replacements are made either rectally or parenterally. Antibiotics are administered throughout. The continuance depends on the non-leakage of the ulcer. Persistence of leakage is determined by the failure of the abdominal rigidity and tenderness to pass off, and a pulse rate that rises or does not fall satisfactorily. An increase of intraperitoneal gas is seen roentgenographically. In cases seen late with marked toxic absorption and peritonitis the need to drain and evacuate the toxic fluid is vital. The operative treatment cannot be forecast to any full extent from the clinical appearance. While simple suture may be enough a gastrojejurostomy has been advocated to by-pass the edema at the pylorus and to ensure better healing. While the added procedure has raised the mortality figures, extensive "follow-up" has discredited this procedure as the best surgical treatment.

While on the European Continent immediate partial gastrectomy has gained considerable support, in England it is felt that such radical measures should be reserved for a later date, the immediate problem in hand being to tide the patient over a matter of life and death.

Drainage is indicated in those cases where the fluid is obviously highly infected and vast in quantity.

Post-operative treatment consists of a Ryle's tube in the stomach for the first 24 hours or more, morphine to allay pain, the maintainence of adequate water and electrolyte balance, antibiotics, breathing exercises and early ambulation.

Sequelae include persistence of peptic ulcer symptoms requiring major surgical attention and re-perforation in about four per cent of cases.

EUSTACE J. DE SOUZA.

PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY EMPHYSEMA, Carter, M. G., Gaenster, E. A. and Kyllonen, A. : New Eng. Jour. Med. **243**: 349-358, 1950.

The authors have found that pneumoperitoneum is an effective treatment for the relief of many of the discomforts of pulmonary emphysema. They accidentally discovered its value when it was found that 3 patients receiving pneumoperitoneum treatment for active pulmonary tuberculosis had severe dyspnea when the treatment was discontinued. They were immediately relieved of dyspnea when the pneumoperitoneum was re-instituted. It was then observed that all 3 patients had marked pulmonary emphysema secondary to contracting fibrosis in areas of tuberculous disease. This observation suggested the possibility of using pneumoperitoneum for the treatment of emphysema not associated with tuberculosis.

Altogether 22 patients were treated, all had dyspnea that was incapacitating for work, and decompensated heart disease was not present, and active tuberculosis, bronchial obstruction and severe bronchiectasis was ruled out. The initial amount of air introduced was 700 to 1000 cc. and stopped when the patient complained of fullness or when he was no longer able to refrain from coughing. Two refills of 500 to 1000 cc. were then given at two-day intervals, and the patient was discharged to return for outpatient refills once every two weeks.

Results : Of 22 patients, 13 spontaneously reported improvement which was marked in 10 and moderate in 3 cases. Subjective improvement was characterised by reduction in dyspnea, increase in exercise tolerance, ability to sleep flat in bed, when previously unable to do so, and ability to raise bronchopulmonary secretions more easily with consequent reduction of cough. One patient was receiving almost constant nasal oxygen therapy, was unable to get out of bed and could not drink a glass of water at a normal rate. Three weeks after beginning treatment he was able to walk into the outpatient department and proudly demonstrate his ability to drink a glass of water at a normal rate.

The most striking effect of pneumoperitoneum was the marked improvement in the force of the cough which cleared the bronchial secretions and removed the constant stimulus to cough. The mode of action could be seen on fluoroscopy. The flattened diaphragm in emphysema is incapable of much further contraction. The pneumoperitoneum restores the arch and the ability to contract forcibly.

E. J. BORGES.

A SIMPLE METHOD OF BRONCHOGRAPHY, Basu, S. P. : Ind. Med. Gaz. **86** : 199-200, 1951.

The author describes a simple method used in the X-Ray Department, School of Tropical Medicine, Calcutta.

The patient is given a pot-iodide mixture the night before to test for iodism. If the report is favourable, he may be submitted to bronchography the next afternoon 3 to 4 hours after lunch.

His throat is swabbed with a 4 per cent cocaine solution till the cough reflex is gone. Then 2 cc. of the cocaine solution is injected into one of the nostrils while the tongue is pulled with a piece of gauze. He is asked to breathe deeply, when as he can't swallow, the solution enters the trachea as indicated by a bout of coughing.

After five minutes when anesthesia is well established, iodised oil is injected into the nostril while the tongue is pulled as before. The patient sits inclined to the right for the first 5 cc., to the left for the second 5 cc., and lies on the right side for the third 5 cc., and on the left side for the last 5 cc. The pictures must be taken as quickly as possible as the patients always complain of a violent spasm of cough.

All food and drink must be prohibited for 2 to 3 hours afterwards to avoid "drowning."

EUSTACE J. DE SOUZA.

EVALUATION OF CLINICAL METHODS IN GASTROINTESTINAL DISEASE. LIVER FUNCTION TESTS IN PEPTIC ULCER, Goldbloom, A. A., Lieberson, A. and Silver, A. : J. A. M. S. **146**: 1593-1594, 1951.

As there has been an increasing mention of liver damage in peptic ulcer the authors reviewed 70 consecutive cases of peptic ulcer in the Beth Israel and Metropolitan

Hospitals, New York City, from this point of view.

The average icteric index was 3.8 and above normal in only 2 cases. One of these at operation was shown to have an obstructive lesion penetrating into the pancreas. The other had gall-stones as well as gastric and duodenal ulcers.

The cephalin-cholesterol flocculation tests average 1+to 2+ and were abnormal in only 6 cases, of which five were complicated ulcers.

The thymol turbidity tests averaged 2.0 units and were abnormal (above 3.5 units) in 3 cases of which only one was uncomplicated.

The sulfobromophthalein tests, total cholesterol, cholesterol esters, total proteins and albumin and globulin ratios were essentially normal in every case.

EUSTACE J. DE SOUZA.

MODERN TREATMENT OF MALIGNANT DISEASE OF THE TESTICLE, Till, A. S. : The Medical Press **226** : 425-427, 1951. 3 references, 1 figure.

The author makes a plea for the correction of the impression that of all malignant diseases that of the testicle has been reckoned the most deadly in its sinister prognosis. With modern methods of treatment some 24 per cent of all cases may now be expected to survive 10 years or more. Malignant disease of the testicle is fortunately rare, about 330 deaths being reported annually as compared with 18000 of carcinoma of the stomach. Tumours of the testicle occur at any age, infants in arms to octogenarians, but the greatest incidence being between 20 and 40. Between 20 and 30 there is a slightly greater likelihood of the tumour being a teratoma, while the peak for seminomata is a decade later. Of the two. the latter is the more common.

Two important predisposing factors are trauma and maldescent. The argument around the pathology of the seminoma. as to whether it is a carcinoma of the seminal epithelium or a one sided development in a teratoid tumour. is still undecided. On clinical grounds two types of tumours are recognised. The teratomata are composed of elements of all three germinal layers. They occur at any age and metastasising both by lymph and blood stream. Their prognosis is not as good as that of the seminoma, but though they are said to be radio-resistant, this is not always the case and the patient should always be given the benefit of radiotherapy.

Seminomata are recognised by the pale homogeneous appearance on section. They spread both by lymph and blood stream, but are characteristically radio-sensitive. In addition to these two types, histologists differentiate chorion-epithelioma and carcinoma apart from seminoma, ut overlap is often present. The diagnosis is not difficult if the possibility is borne in mind.

The common type is that where there is insidious enlargement of the testicle with loss of testicular sensation and a feeling of weight on examination. The "hurricane" type is rare, but rapidly fatal.

A large secondary hydrocele is uncommon but one apparently the size of the idiopathic variety may mask an underlying tumour.

Much has been written of the presence of the prolans or an increase of the 17 ketosteroids in the urine and a positive Aschiem-Zondek test in general denotes a grave prognosis but these tests are subject to many discrepancies.

At present there is fortunately almost complete unanimity about the treatment. The primary tumour should be removed in all cases by simple orchidectomy as soon as possible and this should be followed by deep roentgen ray therapy to the para-aortic and iliac regions whether or not they appear to be involved. Where deposits have occurred at other sites these too must be fully irradiated. Biopsy of the testicle is not advised. The radical orchidectomy practised in the early years of the century has now been abandoned.

Now that radiotherapy has been added to pure surgical treatment of this condition the prognosis has vastly improved. Chorionepithelioma alone remains beyond the scope of therapy, the patient dying early, whatever the treatment. In other conditions, however, prompt diagnosis and efficient treatment offer hope that compares favourably with that of malignant disease anywhere in the body.

EUSTACE J. DE SOUZA.

FLAT FEET, Taylor, R. G. : The Medical Press **226** : 408-411, 1951. 5 figures.

The author points out the fact that some flat feet may be highly efficient as evidenced in the case of barefooted coloured native carriers and in some ballet dancers. Efficient flat feet, however, are freely mobile and supple. The mechanical features of the foot change from the rigid lever during propulsion to the spring cushion during balance. This dual purpose can be served by the foot acting as an arch which is rendered taut by the bowstring action of the muscles during propulsion and the relaxation during rest. The action of the muscles has been well demonstrated by cine radiography in which the calcaneus is seen to move backwards with a piston-like action as the movement of propulsion starts. Each foot represents the half of a pedestal, the two feet together forming a whole pedestal. The outer part of the foot acts chiefly as an organ of balance while the inner part of the foot constitutes the propulsive lever, though it must be remembered that neither part of the foot has either of these functions exclusively.

If, however, after unaccustomed exercise, an occupation that involves prolonged standing or getting up after a prolonged illness, the muscles become fatigued, the duty falls upon the ligaments and fascia to maintain the arches. These structures are not designed exclusively for this purpose. The result is that they become unduly stretched and adhesions occur due to minute hemorrhages. If this condition occurs as the result of a sudden trauma the condition is known as acute foot strain, while if insidious in onset it is termed as chronic foot strain. It must not be forgotten that in the elderly some degree of ischemia may give rise to similar symptoms. Relief can be obtained by rest and active and passive exercises but if pain still persists, gentle manipulation under general anesthesia should be carried out and may be repeated if necessary. This should be followed by a course of faradic foot baths and foot exercises to restore proper function. The use of an arch support is an unwise measure as it relieves the muscles of work and thus encourages atrophy. Occasionally osteoarthritic changes in the tarsal joints may require arthrodesis.

Congenital flat foot is a difficult condition to treat where the foot is grossly flattened and boat shaped. The deformity if recognised early may be treated by repeated manipulations and plaster immobilisation. Excision of the head of the talus with an osteotomy of the anterior end of the calcaneous and appropriate moulding in plaster is the only measure that can be carried out later. Often, however, the treatment of choice is a well fitting surgical boot.

The infantile flat foot is a mild talipes calcaneo-valgus. The condition is best treated by a Thomas' elevated and prolonged heel. In more severe cases an outside iron and inside T-strap is used in addition.

Adolescent flat feet present in rapidly growing children who are subject to fatigue, prolonged standing or under feeding, and are often associated with bow legs or knock knees, the treatment is a general one, including rest, alternate sitting and standing foot exercises and inner wedges to the heels.

Spasmodic flat foot or peroneo-extensor spasm occurs in adolescents between 14 and 18 years who have been suddenly subjected to laborious work involving prolonged walking or standing. The spasm fixing the foot in valgus has been shown by Ellis to disappear with the injection of proctocaine. The treatment consists in abolishing a septic focus, if present, and manipulation under general anesthesia followed by immobilisation in plaster. Congenital talo-calcaneal synostosis, syndesmosis or synarthrosis may resemble spasmodic flat foot. The best treatment is arthrodesis of the sub-taloid and mid-tarsal joints.

Congenital calcaneo-navicular synostosis also produces a rigid valgus foot. Resection of the calcaneo-navicular bar occasionally gives good results but some patients require surgical shoes while for others the best treatment is sub-taloid and mid-tarsal arthrodesis.

EUSTACE J. DE SOUZA.

PEDIATRICS

TRIALS OF ORAL STREPTOMYCIN FOR INFANTS WITH NON-SPECIFIC GASTROENTERITIS I. TRIAL AT THE CITY HOSPITAL, EDINBURGH, London, G. M., and McNeil, M. M. : *B. M. J.* **2** : *667-770, 1951.*

Previous papers concerning the treatment of infantile gastro-enteritis by streptomycin have reported contradictory results. In this paper, 24 cases of non-specific infantile gastroenteritis from the gastroenteritis unit in Edinburgh, were treated with oral streptomycin and their results compared with a control series receiving no oral antibiotics. All the cases were of the endemic type. The babies had been artificially fed before admission, with one exception. All the babies were under 13 months of age. Eight trial cases had parenteral infections on admission. The assessment of the severity of the disease was purely clinical, those requiring intravenous therapy within 24 hours of admission were categorized as severe, if not—as mild. Fourteen cases received oral streptomycin in the dosage of 1 Gm. daily in divided doses for 6 days, and 10 cases were given 2 Gm. daily in divided doses for 12 days. Routine treatment was similar in all cases (half strength Ringer's lactate solution, 5 per cent glucose, graduated milk feeding, vitamin C and B complex). In the trial series 12 babies received sulfadiazine. The average number of days of diarrhea in the trials and the control series was 7.5 to 7.8 days respectively. The average number of days for full clinical recovery was 26.6 days in the trial series and 26.1 days in the control group. The authors concluded that the drug did not influence the course of the disease any more or any less favourably than the treatment given to the control group. There appears, therefore, to be no reason to prefer oral streptomycin to sulphadiazine in the treatment of non-specific gastroenteritis.

ERIC COELHO.

HYPOPROTEINOSIS OF CHILDHOOD, Lynch, H. D., and Snively, W. F. : J. A. M. A. **147** : 115-119, 1951. 11 references.

The authors encountered a repetitious combination of complaints in office practice in children and attributed it to a syndrome which they called "hypoproteinosis of childhood." The writers give a preliminary report based on purely clinical observation and cite 9 cases. The symptoms met with in this syndrome were as follows :—Anorexia, failure to gain weight, vomiting, constipation, increased susceptibility to infections, dental caries and anemia. An explanation of each of these symptoms is given in some detail. Owing to lack of laboratory facilities only routine blood examinations were done and the only significant evidence observed was the presence of a hypochromic anemia. The diagnosis of hypoproteinosis was based on the dietary history and the symptomatology. Typically, there was a history that the child was a good milk drinker and that he does not eat at mealtime. The authors attribute low protein diet as the etiological factor. This is certainly understandable in the poverty stricken and to add to it the relatively high cost of protein foods as compared to the inexpensive starches and sweets. The basic reason, according to the writers, is the general lack of understanding by parents of the fundamentals of nutrition. An effective management necessitates not only a diet ample in protein but also educational and psychological facets as well.

ERIC COELHO.

DERMATOLOGY.

TREATMENT OF CHRONIC CUTANEOUS PROBLEMS WITH CALCIFEROL, Foldberg, L .C. and Dexter, H. L. T. : Arch. of Derm. and Syph., 63 : 729-739. 1951

Vitamin D_2 or calciferol was tried by the authors in several chronic skin disorders which did not respond to usual routine treatment. The material used was a highly potent calciferol (vitamin D_2, 1250 units per drop) in propylene glycol. The dose varied from 2 drops (2,500 units) three times a day to maximum of 40 drops (50,000 units) three times a day depending upon the age and individual reactions. For the correct appraisal of the therapy, the drug should be given at least for 3 months before it is abandoned. Patients usually improve in the first 3 weeks of treatment. It is advised to establish a maintenance dose for each patient to prevent relapse.

This treatment was tried in : (1) atopic dermatitis. (2) chronic eczematoid dermatitis, (3) psoriasis vulgaris, (4) acne conglobata, (5) lupus erythematosus, (6) granuloma annulare and (7) mycosis fungoides. Favourable results obtained in atopic dermatitis are quite impressive. Mild local therapy should be continued inasmuch as calciferol is not a specific and is far from cure. One patient with acne conglobata responded well. In numbers (2) and (3) results were not encouraging except in a few cases, but authors recommend further trials in these cases. It was non-beneficial in the rest.

As for the reactions to the drug, they are divided into two groups : (1) symptoms of toxicity and (2) chemical manifestations of toxicity. The former includes nausea, vomiting, abdominal pain, loss of appetite, fatigue and weakness, frequency of urination, nocturia, thirst, loss of weight and joint pains, under the latter are included albuminuria, hyper-calcemia, alkaline phosphatemia, and increase in blood urea nitrogen. The authors had carried out necessary investigations in all their hospital patients, before, during and after the institution of treatment. On the regime followed by the authors only two patients had mild reactions. This emphasizes the safety of the treatment.

As to the nature of vitamin D_2, the authors state that it is a chemically pure and uniform crystalline product. It is one of the products formed by irradiation of ergosterol, others being lumisterol. They together constitute vitamin D_1. The action of calciferol is not yet definitely determined. Curtis and his group state, "we feel its main effects may be due to removal of phosphorus from soft tissue and bone." Charpy insisted on simultaneous administration of calcium which the present authors don't think necessary. In conclusion, authors recommend further trial of the drug in atopic dermatitis.

T. K. MEHTA.

ORAL ADMINISTRATION OF PROCAINE WITH ASCORBIC ACID, WITH SPECIAL REFERENCE TO THE THERAPY OF PRURITUS, Luddecke, M. : Arch. of Dermat. and Syph. 64 : 9-11, 1951.

Procaine has been used in the past for the treatment of allergic disorders, many times with success. It was then used intravenously. Its oral use is a novel procedure introduced by the author for the first time excepting one paper by Schapiro and his associates. The author used it in combination with ascorbic acid in the treatment of various disorders particularly those with an allergic background and having itching as a principal symptom. The combination of procaine and ascorbic acid was actually administered to 5 patients. But for one case of atopic dermatitis, all showed dramatic improvement both subjectively and objectively. In the other five, procaine was given orally in combination with ephedrine and methapyrilene. All were relieved of the trouble. The dose of procaine varied from case to case, but now the author intends to give 250 mg. of procaine hydrochloride and 150 mg. of ascorbic acid per tablet. It is of great interest to note that side-effects due to orally administered procaine combination were nil in the author's series of 10 cases. This is remarkable in view of the fact that doses of as much as 2,400 mg. of procaine were given daily. The mechanism of action is not yet clear. It is a mere speculation that a breakdown product of the digestion of procaine may be responsible for the beneficial results. Three representative case records are included in the text plus a table containing the results of oral procaine in all 10 cases.

T. K. MEHTA.

ACRODERMATITIS PUSTULOSA PERSTANS : A METHOD OF TREATMENT, Fishman, H. C : Arch. of Dermat and Syph., **64** : 56-57, 1951.

The author had 10 cases of this usually recalcitrant disease of the palms and soles. These cases showed a typical clinical appearance of tiny, deep vesiculo—pustules, studding erythematous, slightly scaly patches on the palms and soles. After failing with usual measures of therapy *viz.*, sulfonamides, penicillin, removal of septic foci, x-rays and other advocated measures, the author hit upon an entirely novel method of treatment arrived at by trial and error only. Further, he had such unusual success with this new therapy that he could not help reporting the method of treatment so that more widespread evaluation might be undertaken.

The therapeutic regime consisted of the oral administration of 150,000 units of vitamin A, frequent application of 5 per cent coal tar solution in a water soluble base and the weekly administration of suberythema doses of radiation from a cold quartz lamp. The duration of treatment varied in different cases from 2 weeks to 2 months and more. All the 10 cases of the author cleared up dramatically with above regime and remained well for months together later. While vitamin A seems to be the major factor in clearing the lesions, a failure of response to vitamin A alone in one patient plus the fact that the coal tar solution preparation makes the patient much more comfortable, led the author to use the combination of all three agents. Three illustrative case histories are reported with the text.

T. K. MEHTA.

PIGMENTARY PURPURIC DISEASES OF THE LOWER EXTREMITIES, Kierland, R. : Med. Clin. of North America, **36** : 457-462, 1951.

Under the above title the author has discussed the following conditions, (1) " progressive pigmentary disorder " of Schamberg ; (2) "pigmented purpuric lichenoid dermatitis " of Gongerot and Blum, (3) angioma serpiginosum and (4) "purpura annularis telengiectodes" of Majocchi. After discussing fully clinical features, histopathology and differential diagnosis, he makes a strong case for considering all these disorders as merely simple varieties of the same basic pathologic process. They are manifestations of increased capillary permeability and fragility, the cause of which remains unknown. All these disorders are characterized by the common feature of purpuric spots on the legs. They are not serious or severe and don't cause any discomfort to the patient. Since there is a basic pathology for the deposition of blood pigment in the dermis the author proposes that all these conditions of pigmentary purpuric eruptions should be included under the term "Simple Hemosiderosis". The treatment is directed towards reassurance, and towards removal of any possible etiologic factors discovered, such as treatment of venous insufficiency by the use of supportive bandages, the administration by mouth of rutin with or without vitamin C, and the use of antihistamine drugs if an allergic basis could be detected.

T. K. MEHTA.

PATHOLOGY

CULTURAL CHARACTERISTICS OF THREE GRANULAR-CELL MYOBLASTOMAS. Murray, M. R. : Cancer 4 : 857-865, 1951

The author gives an account of three granular-cell myoblastomas which were cultivated *in vitro*. Two of these tumors were in the breast and the third was in the vastus lateralis muscle. Microscopically all the tumors appeared benign, and were of the type designated as 'uniform'. It has been observed that in culture, even this 'uniform' type of myoblastoma might become much less uniform, and more pleopmorphic *in vitro* than it appeared *in vivo*. There was little doubt that the cultured cells were tumor cells, because they retained one or more distinctive characteristics of the granulomyoblasts. Comparing the growth characteristics of these three tumors *in vitro*, with the embryonic and adult skeletal muscle, regenerating muscle, rhabdomyomas, and rhabdomyosarcomas, as well as with other types of normal and neoplastic cells in tissue culture, the author concludes that the granular-cell myoblastoma cultures bear a greater resemblance to cultures of various forms of skeletal muscle, normal and neoplastic than to cultures of other tissue types to which their origin has sometimes been attributed.

M. V. SIRSAT.

EPITHELIAL METAPLASIA IN "PROSTATIC INFARCTION", Mostofi, F. K. and Morse, W. H. : Archives of Pathology 51 : 340-345, 1951.

The diagnosis of squamous cell carcinoma of the prostate is frequently made, in spite of the fact it is a rare lesion, mainly because squamous metaplasia occurring in prostatic infarction simulates squamous cell carcinoma. The present study is based on 50 specimens seen at the Armed Forces Institute of Pathology Washington, D.C. In this series, epithelial metaplasia was an outstanding feature and was observed in 47 specimens of prostates. In 3, it was absent. In 8 cases in which metaplasia was noted, there was a co-existing adenocarcinoma. In 10 cases a diagnosis of carcinoma was made erroneously. It was observed that the lesion was always situated in a hyperplastic nodule. There was a definite sequence of development of the lesion and this has been demonstrated by the authors by means of photomicrographs. The epithelial changes which occurred in prostatic infarction were not of a cancerous nature and the authors have emphasised the fact that an area of infarction should not rule out the presence of carcinoma elsewhere in the prostate. In 8 of their cases, adenocarcinoma co-existed with infarction and squamous metaplasia. The mechanism of the squamous metaplasia, and the length of time that intervenes before the change becomes apparent in infarction of the prostate, was obscure. Squamous metaplasia which occurred in the so-called infarction of the prostate was associated with an area of necrosis or scar, and this lesion must be distinguished from squamous cell carcinoma.

M. V. SIRSAT.

PUBLIC HEALTH

ALCOHOLISM : A PUBLIC HEALTH PROBLEM, : CHRONICLE OF THE WORLD HEALTH ORGANIZATION 5 : 231-235, 1951.

The recognition of alcoholism as a public health problem rather than a social disorder and the noteworthy progress in bringing this condition into the realm of scientific research enabled the Subcommittee on Alcoholism of the WHO Expert Committee on Mental Health to recommend to national health administrations practical measures to prevent and treat alcoholism. Besides the definition of the terms "alcoholism," tolerance and "cure" from a clinical standpoint there are three recognisable stages in the development of alcoholism. In the first stage termed "symptomatic drinking" alcohol is taken as an anodyne for a current physical, psychological or social problem. The second is the "addictive" stage and in the third, actual organic or psychic disease appears.

The extreme variety of drinking habits and customs and the numerous kinds of alcoholic beverages in different countries, makes statistical evaluation of the problem extremely difficult.

The prognosis and treatment depend upon the stage to which addiction has reached. In the first stage it may be possible to treat psychiatrically the underlying cause of the drinking, which if successfully accomplished may enable the patient to resume such moderate controlled drinking as may have been his habit before the alcoholic episode. In the second stage it is impossible to attain moderate drinking and the aim of therapy must be at total abstinence. In well developed countries there are usually available, facilities for advanced cases of alcoholism especially for those that show advanced organic or psychological damage. The real need is for out-patient dispensary services for treatment of the earlier stages. This should have the orientation of a medical institution with the services of a psychiatrist interested in the problem of alcoholism.

Research is needed to delve into the psychological or physiopathological factors underlying addictive drinking.

Certain drugs may prove a valuable adjunct to psychological as well as social therapy. Chief among these is tetraethylthiuramdisulphide which causes severe somatic reactions if alcoholic beverages are taken while the patient is on a maint-tenance dose. In more advanced cases some form of aversion therapy may be more valuable. Hormones like ACTH and cortisone have been reported to be useful in treating delirium tremens, acute alcoholic intoxication and even Korsakoff psychosis.

Attention is also called to the lack of proper education in this subject on the part of the physician, nurse and medical social worker, and compulsory inclusion of this subject in relevant curricula is advocated. The difficulties in the way of research in this field is stressed and the classification and dissemination of information on this subject is recommended.

The work of lay societies particularly that of "Alcoholics Anonymous" is commended.

EUSTACE J. DE SOUZA.

Physicians, when tending upon their patients, should make their health their first object. So gentle and sympathizing should be their dispositions and manner in the apartment of the sick that pain and distress should seem suspended in their presence. So exhilarating ought their visits to be that hope should follow their footsteps, so salutary their prescriptions that death should drop his commission in combat with their skill.

—William Beaumont, Medical World, 74 : 693, 1951.

FOR PRACTITIONERS

HEMATURIA

D. D. Vora

Larcom and Carter in a study of single voided urine of 3,000 healthy men found erythrocytes in 2.7 per cent of specimens—2 per cent showing 2—3 erythrocytes per high power field of the microscope and 0.7 per cent showing 4—5 erythrocytes per high power field. They concluded that presence of more than 2 erythrocytes in each high power field may indicate an increased or abnormal loss of erythrocytes from the urinary tract.

Hematuria is of two types :—(a). microscopic and (b) macroscopic or gross hematuria. This is an arbitrary classification as any condition in which microscopic erythrocyturia may occur, gross hematuria can also appear.

Hematuria may be associated with or secondary to (1) systemic disease *e.g.*, diseases of blood or blood-forming organs as thrombocytopenic purpura, leukemia, hemophilia, (2) cardiovascular diseases, *e.g.*, bacterial endocarditis, embolism from mitral valve disease of the heart, malignant hypertension or rarely congestive cardiac failure, (3) acute conditions, such as, small-pox, yellow fever and scarlet fever, (4) deficiency diseases, like scurvy, vitamin K deficiency (5) administration of drugs like heparin, dicoumarol, turpentine, cantharides, sulphonamides, carbolic acid, and occasionally, administration of anti-tetanus serum.

Hematuria may be due to disease of organs adjacent to the urinary tract, such as acute appendicitis, acute salpingitis, acute diverticulitis of the colon or malignancy involving neighbouring structures.

Commonly hematuria is the result of the diseases of the urinary tract. Among the conditions are :—(1) Congenital malformations, *e.g.*, polycystic disease of the kidneys, or obstruction at the uretero-pelvic junction, (2) trauma directly involving any of the organs of the urinary tract, (3) acute and chronic glomerulonephritis, (4) acute or chronic pyelitis or pyelonephritis (5) acute or chronic cystitis, (6) stone in the urinary tract from kidney downwards to urethra (7) tuberculous infection of the urinary tract, (8) hydronephrosis or pyonephrosis (9) benign vascular growth or a malignant growth either in the kidney, renal pelvis, ureter, bladder, prostate, and urethra (10) Bilharziasis. This is a condition commonly found in Egypt.

An essential hematuria is diagnosed when a thorough clinical examination and a detailed investigation fails to point either at the etiology or the site of the blood loss.

Either a gross hematuria or a persistent or intermittent microscopic hematuria present in the urine of a male or in catherised urine of a female should lead to a thorough investigation of the patient.

The age of the patient, a detailed description of the nature of hematuria, and a thorough clinical examination can help to locate the site of blood loss as well as the etiology of it, accurately, in a majority of cases.

In infancy, the commoner causes of gross hematuria are congenital obstruction at the uretero-pelvic juncture, Wilms' tumour, sarcoma of the bladder or prostate gland. In young adults and persons up to the age of 40 years, gross hematuria is commonly a manifestation of infection like cystitis or pyelonephritis, renal or ureteral stone. After the age of 40 years neoplasms or benign prostatic hypertrophy is considered commonly.

In males, it should be determined whether the hematuria is at the beginning, the end, throughout or independent of mictuirition. Initial hematuria indicates the lesions of the prostate or prostatic urethra. Total hematuria indicates the blood to be from the kidneys or the ureters. Terminal hematuria may result from neoplasms of the bladder, or very rarely, from the lesions of the prostate.

Palpation of the abdomen may reveal a renal lump. It may be due to Wilms' tumour in an infant, or due to polycystic disease of the kidneys, when it is associated with hypertension, or due to hydronephrosis or pyonephrosis. Per rectal digital examination may reveal a vesical stone or benign hypertrophy of the prostate or its malignancy.

The investigations carried out to elicit the cause of hematuria are routine examination of the urine, plain skiagram of the urinary tract, pyelography, and endoscopic examination.

During the microscopic examination, the presence of other elements of the urine gives an indication of the site of blood loss, *e.g.*, the granular casts point to the kidneys to be the site of hematuria ; the pus cells and renal pelvic epithelial cells—the acute or chronic infection of the pelvis. The presence of large amount of calcium oxalate crystals indicate stone in the kidney. Presence of mucous in the urine, besides bladder epithelial cells and pus cells, with large amount of phosphates, indicate stone in the bladder.

Plain X-ray of the urinary tract may show opacity in the shadow of either kidney and the resemblance of its shape to that of the renal pelvis with its calyces indicates a stone in the kidney. It may be indicative of tuberculosis of the kidney, if the patient has other toxic symptoms of tuberculous infection, *e.g.*, low fever, unexplained loss of weight. A vertical spindle-shaped shadow in the line of the ureter points to a ureteric stone. The stone in the bladder is round and is above the symphysis pubis.

Excretion pyelography helps to confirm a ureteric stone besides showing the damage to the kidney function. It outlines also the urinary bladder and helps to show a growth or diverticulum.

Endoscopic examination of the urethra with a urethroscope may reveal an angioma of the urethra. The cystoscope will show the stone of growth or a diverticulum of the bladder. Besides, it gives the facility of taking biopsies from the bladder. Through the cystoscope the function of each kidney can be studied by observing the flow of the urine or a dye like methylene blue or indigo-carmine excreted by the kidneys when injected intravenously. The cystoscope also helps to catheterise the ureters individually and thus the site of the affected kidney or ureter is easily determined. Ascending pyelography is carried out, if necessary, through cystoscope.

Hematuria should be distinguished from hemoglobinuria in which the urine held in the glass is transparent or translucent, as compared to the urine of hematuria which is opaque. Also red discolouration of the urine due to drug or dyes should not be mistaken for hematuria.

The treatment of the hematuria is carried out according to the cause. In the acute attack, the patient should be quietened with an injection of morphine $\frac{1}{4}$ grain. and should be put to complete rest in bed till about 48 hours after the bleeding subsides. The patient should be encouraged to drink plenty of water by mouth.

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BRONCHIAL ASTHMA IN THE OLDER PERSONS

D. D. Vora

The first attack of asthma can occur at any age. but it occurs less commonly after the age of 25 years. It is so uncommon for the first attack of asthma to occur after the age of 50 years that a majority of clinicians always try to rule out the heart diseases as the cause and treat the case as dyspnea due to left sided failure of the heart. Cooper as well as Maxwell do not mention the age when the first attack of asthma occurs. However, Young and Beaumont mention in Practice of Medicine edited by Price that the first attack of asthma is rare after the age of 25 years. Tuft cites Coke, who in a series of 1000 asthmatics found only 20 patients (2 per cent) above the age of 60. He also quotes Rowe and Rowe who in a study of 1,232 patients, found only 72 patients in whom asthma began after the age of 50,—an incidence of 5.85 per cent. The same author quotes Fuchs who studied 200 asthmatics and found that the age of onset at the initial attack was given as past 50 in 27, or 13.5 per cent.

Etiology :—

Heredity. The significance of hereditary predisposition to asthma decreases progressively after the age of 20. The asthma in the older people usually is not accompanied with such marked sensitivity to specific allergens as in the younger persons, nor is it associated so often with other atopic manifestations such as. eczema, migraine or hay fever.

Acquired sensitivity to allergens. The older people develop sensitivity to inhalants, foods, drugs, or bacterial allergens, or to internal causes like endocrine or psychosomatic. to the same extent as young. The asthma thus provoked may become the starting point for a new line of allergic offspring in subsequent generations. The inhalant allergens may be various occupational dusts ; it may be anthracosis or card room worker's asthma. Allergy to food does not seem to be a major etiological cause. for generally food allergies are overcome during maturity. Generally, the respiratory infections may precipitate an attack of asthma in the older people for the first time. Drugs of biological origin like the sera, if given in an elderly person for the first time, may precipitate an acute attack of bronchial asthma, as it happens in the younger persons. The endocrine cause is not yet fully confirmed as the cause of the asthma in the elderly, though it is known that in some women an already existing asthma becomes worse at or after the menopause. The elders react to emotional strain in the same way as the young people and a severe strain in an old man may be the cause of the first attack of asthma. But when neither of the cause could be determined and when the attack is the typical attack of asthma it is best known by the term idiopathic. which describes the situation more faithfully.

The nasal factor so commonly considered in the younger people is rarely considered even when there is objective evidence to that effect. As the correction of the same does not help at all in alleviating the condition.

Clinical Diagnosis—

The clinical examination reveals the classical picture of bronchial asthma. But a thorough clinical examination supported by X-ray of the chest, total and differential white blood cell count, sputum examination by concentration method, and electro-cardiogram, is carried out to exclude the following causes of the dyspnea :—

Mediastinal tumours of neoplastic. aneurysmal, or lymphatic origin. Generally they cause unilateral wheezing and there is stridor associated with it. X-ray establishes the diagnosis with certainty.

Cardiovascular diseases associated with dyspnea. Here there is objective evidence of the cardiovascular disease *e.g.*, enlarged heart, hypertension, valvular diseases, or recent or past coronary disease. The attack occurs generally soon after the patient goes to bed and there is a history of exertional dyspnea. Patient feels better on sitting up in the bed and responds well to restriction in the diet, and organic mercurial diuretic and digitalis by mouth.

Acute or chronic bronchitis. Here the onset is not so sudden and in the acute condition is associated with a rise of temperature. Chronic bronchitis is distinguished from asthma with great difficulty.

Eosinophilic—the white blood cell count decides the diagnosis.

The skin sensitivity tests are of not much use in the elders as the skin sensitivity is low in them and they are not good indicators of the allergy that may be existent.

Treatment:—

Diet. Dietetic restrictions should be carried out when the food is the etiological factor. It is better to start with milk diet and gradually add the various articles one by one and to note down when the asthma recurs. The same article should be then withheld and further trials carried out to see if the asthma stays away. Thus the incriminating article if detected should be avoided if possible for ever.

The nasal infection is better dealt with conservatively.

Where there are signs of acute infection in the respiratory tract penicillin or any of the recent antibiotics should be used generously till the infection is completely controlled.

During the acute attack adrenaline or epinephrine is given. High blood-pressure if present should not deter the physician from giving adrenaline or ephedrine. It does not raise the blood-pressure further in the asthmatic, but lowers the blood-pressure which is generally raised by the vascular strain induced by the acute asthma. But there is one drawback to the use of epinephrine in the elderly patients, specially those with prostatic hypertrophy. It causes vesical tenesmus and retention of urine. This is transient, but should always be borne in mind while administering epinephrine to such patients lest a surgical complication arising fresh may be thought of. Aminophylline is used intravenously diluted with glucose or glucose-saline and given slowly. This may cause fall of blood-pressure if given rapidly.

To ward off the attack or to minimise the acute attacks the bronchial secretions are kept liquefied by constant administration of iodides in doses of 10 to 20 grains three to four times a day. Even higher doses are recommended.

Alcohol is recommended though it does not relieve the acute attack. It is supposed to have a tonic and supportive action. Barbiturates or morphine should be given minimum possible as the older people do not always tolerate them easily.

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ANTITUBERCULIN VACCINATION. Editorial. The New Eng. J. of Med. 245: 230-231, 1951.

Convincing proof of the success or failure of protecting children against tuberculosis by vaccination has been difficult because of the lack of exact clinical experiments, for intentional exposure of a child or group of children to tuberculosis is not in keeping with modern ethical codes. However, in Italy, during the stress of the last world war, an unintentional clinical experiment took place and has been recently reported in an Italian pediatric publication.

In Italy, Petragini's anatuberculin (killed tubercle bacilli), instead of B.C.G., is the prevailing means of vaccinating children against tuberculosis.

During the war years, an overcrowded institution for babies near Venice was the site of an epidemic of active tuberculosis. The massive exposure was believed to be due to the admission of babies with active tuberculosis and to their being left in close contact with other babies in small rooms. Of 134 babies in the institution, 54 had been vaccinated with Petragini's anatuberculin ; 78 were unvaccinated. Of the 54 vaccinated infants, 9 had developed within one year a tuberculous infection, all being of the hilum glands ; there were no deaths. Of the 78 unvaccinated infants, 21 developed tuberculosis, 9 having hilar lymphadenitis and the other 12 exudative lesions—acute miliary, meningeal or active pulmonary ; 11 died.

The epidemic had brought about an unintentional but quite conclusive experiment, which indicates the efficacy of Petragini's anatuberculin in protecting infants against tuberculosis. Even infants who received the prophylactic injections as short a time as one month prior to the epidemic appeared to receive protection.

D. D. VORA.

REVIEW OF NEW DRUG THERAPIES IN THE TREATMENT OF ALCOHOLISM, Thimann, J.: The New England Journal of Medicine 244 : 939-941, 1951.

In recent years two new drugs have been added to the physician's armamentarium in the fight against alcoholic addiction.

The first is tetraethyl thiuram disulfide, commercially known as Antabuse. It has the property of oversensitizing the body to alcohol, as a result, a person who has taken a certain amount of the drug will, if alcohol is consumed a few hours or on the following day, experience several kinds of rather unpleasant or even alarming symptoms and signs. They are a feeling of heat in the head concurrent with marked vasodilatation spreading to the neck, chest, arms and sclerae. There is pressure and throbbing in the head, palpitations and dyspnea. There may be acceleration of pulse and fall in the blood pressure. The fall in the blood pressure may cause alarming symptoms and if the amount of the drug is large, even death. Hence it is advised to test the sensitivity of the patient by a test dose and should be thoroughly examined before giving the treatment. Preferably, the treatment should be carried out in a hospital.

Another drug is adrenal cortex extract (ACE). This is based on the observation of Tintera and Lovell who found a frequent association of hypoadrenocorticism and chronic alcoholism. They have assumed that it was constitutional in asthenic alcoholics with soft, smooth faces and overdeveloped breasts, who are characterised by hypoglycemia, low 17-ketosteroids and reduced androgens. In those alcoholics, who are physically and biochemically well developed, the adrenal cortical dysfunction was acquired through prolonged and excessive alcohol dysfunction. In such persons, there was lymphocytosis in the acute stage of intoxication—an indication of adrenal deficiency. Hypoglycemia was seen in the abstinent intervals. Chronic alcoholics need sweets or a milk shake several hours after meals. A marked craving experienced is satisfied by either of the things. This is thus achieved by giving adrenal cortex hormone injections, which mobilize glycogen from tissue protein and raise blood sugar and improve liver function. For the acute alcoholic state, hospitalisation is necessary for several days. The authors mentioned above, give 30 cc. of adrenal cortex extract intravenously in three doses on the first day, 20 cc. in two doses on the second, and for the next three days a single dose of 5 or 10 cc. This is followed by out-patient department treatment which consists of 2—5 cc. of adrenal cortex extract twice a week intramuscularly for three weeks, then weekly for several months. With this is a recommended high fat diet, moderate protein, low carbohydrate diet, insulin for anorexia, and testosterone for hypogonadism.

Smith used adrenocorticotrophic hormone (ACTH) in the acute alcoholic stage and found it useful. It was used in delirium tremens and Korsakow's psychosis, and found to be of no use in the latter condition.

The sucess of Antabuse and adrenal cortex extract are almost equal in establishing unqualified abstinence. But the categories of improvement and failure have different values : 19.9 per cent improvement and 28.5 per cent failures with Antabuse as against 4.5 per cent improvement and 40.9 per cent failures with adrenal cortex extract. This is indicative of a preponderance of the psychological factor in Antabuse in contrast to the predominantly pharmacological mechanism in adrenal cortex extract.

D. D. VORA.

LOCAL APPLICATION OF CHLORAMPHENICOL, Coppleson, V. M. Lancet 2 : 65-66, 1951.

Recent clinical trials of the local application of chloramphenicol ('chloromycetin') suggest that in infected wounds, ulcers, burns, and even wound infected by gas-forming organisms, local application is superior to administration by mouth.

It is used as a lotion to irrigate wounds and cavities by adding the contents of 2-4 capsules (500-1000 mg.) to 5 cc. of distilled water. It is also used as a powder. Pure chloramphenicol has been used for small ulcers, or placed in operation wounds. For surface wounds or larger areas a dusting-powder of the contents of 2-4 capsules (500-1000 mg.) to 1 oz. of pulv. amyli and zinc oxide, equal parts, has been used. At present trials are going on of the following :—

Chloramphenicol	500-1000 mg.
Lactose	1 oz.

It is used as an ointment, 500-1000 mg. in 1 oz. of plain petroleum jelly. The clinical trials conducted at present indicate that local application of chloramphenicol is the most valuable method, and that the antibiotic is probably more efficient when applied directly to open wounds than when administered by mouth.

D. D. VORA.

"SORE THROAT" IN GENERAL PRACTICE, Landsman, J. B., Grist, N. R., Black. R., McFarlane, D., Blair, W. and Anderson. T.: B. M. J. 1 : 326-329, 1951. 1 Fig., 2 refs. (Quoted from Abstracts of World Medicine, 10 : 65. 1951.)

The authors studied a series of 95 cases of "sore throat" occurring in general practice in an urban district, noting certain points of epidemiological interest, and in view of recent criticism, observing the effects of treatment with sulphonamides. Uniform records of the duration of signs and symptoms were kept, and in all cases cultures were taken from the throat and post-nasal space, the cases being thus divided into two groups—those with normal flora, and those with varying numbers of B-hemolytic streptococci on culture. Less than one half of the cases (46 per cent) were classed as streptococcal in origin, an observation of some interest and importance since it is a common misapprehension that acute tonsillitis is almost always of streptococcal origin.

In streptococcal cases, headache, anorexia, vomiting, sweating, chills, and rigors predominated, whereas in the other group there was a predominance of symptoms more clearly referable to the respiratory tract, such as sneezing, stuffy rhinorrhoea, and cough, and the illness took a rather milder form and tended to be more common in childhood.

An attempt to define the probable bacteriological cause before the result of the throat swabs was known, resulted in frequent errors in both groups.

Three different tablets, identical in appearance, were used in treatment, consisting of sulphanilamide (0.5 Gm.) (26 cases), "sulphatriad" (0.5 Gm.) (26 cases), and lactose (0.5 Gm.) (43 cases), and the practitioner in clinical charge did not know which he was using. (No mention is made of dosage.) The main signs and symptoms of which the duration was noted were fever, faucial edema, and pain. There was little difference, and certainly no statistically significant difference, between the average duration of any of these, whichever tablet was given, there being no indication that either of the sulphonamide tablets was superior to the presumably inert lactose tablet. Complications were few and there was little difference between the effects of treatment in this respect.

The authors conclude that their findings do not support the view that the sulphonamides exert a beneficial effect in the treatment of the acute "sore throat" and that in view of the fact that in about half the cases a streptococcal etiology was unlikely, the use of drugs which have definite and known dangers is unnecessary, besides being expensive.

D. D. VORA.

CRITICAL EVALUATION OF ANTIHISTAMINIC DRUGS IN THE COMMON COLD, Fabricant, N. D.: Arch. Otolaryng., 52 : 888-899, 1950. 22 refs. (Quoted from Abstracts of World Medicine, 10: 97, 1951).

"As a result of extravagant and irresponsible claims on behalf of antihistamine drugs, the American public has been deluded into spending huge sums of money on the 'sensational new discovery that kills colds in hours.' It will continue to do so until it is educated by alert physicians to the foolishness of such practice. "The author amplifies these remarks with a list of dangerous complications produced by the antihistamine drugs in patients taking them for the common cold : 3 cases of hemolytic anemia, 3 of agranulocytosis, rashes, cardiac excitation, headache, tinnitus, fever, as well as the better known effects such as drowsiness and dizziness. In a survey by 247 physicians, 223 reported having noted side-effects of antihistamine drugs in their patients.

There is no real evidence that allergy is mainly responsible for the common cold. Most of the writers who advocated these drugs for the common cold failed to differentiate between the infective cold and vasomotor disturbances of allergic conditions. Fully controlled studies in the United States and in Great Briton have demonstrated the failure of antihistaminics in the treatment and control of the genuine "common cold." To these studies is now added a carefully controlled research on 213 students. It is concluded that "antihistaminic drugs do not prevent, abort, shorten, curtail, reduce, or stop the common cold. It was observed that antihistaminic drugs are no more effective than placebos in aborting a cold and that there is no validity in the contention that antihistaminic drugs are more effective if taken within a short time after the start of a cold."

D. D. VORA.

ANORECTAL SYNDROME AND OTHER MILD SIDE-EFFECTS OF TERRAMYCIN, Willcox. R. R.: Lancet, 2 : 154-156, 1951. 1 table. 3 refs.

The Council of Pharmacy and Chemistry of the American Medical Association now requires that all bottles of the oral antibiotics 'aureomycin,' chloramphenicol, and 'terramycin' carry a warning to the effect that, when susceptible bacteria are suppressed by their use, yeast-like organisms—e.g., *Monilia* (*Candida*) *albicans*—may appear. Seventy-four patients were treated by the author with terramycin. 36 patients were given only 2 Gm. in single, double, or multiple doses. Side effects were noted in only four (diarrhoes, heartburn in 1, and rectal soreness in 2).

38 patients were treated with 2.25—19.25 Gm. in 2-14 days, most of them receiving 5-9 Gm. in 5-7 days. 25 patients had no upset, but 13 patients exhibited 22 side-effects, but these necessitated termination of treatment in 2 cases. Diarrhoea was noted in 9, nausea in 4, anorectal syndrome in 5, and waterbrash, headache, drowsiness, and sore-throat in 1 each.

The anorectal syndrome was noted in 7 male patients. The anorectal syndrome consists of burning, soreness, and pruritus of the rectum and anus following the oral administration of terramycin and it may be associated with redness of the anus and of the surrounding skin, but may be without signs. It differs from the diarrhoea and other signs of gastro-intestinal irritation, which appear at once and subside when the drug is discontinued, in so far as it does not usually appear until the drug has been administered for 5—7 days and may persist for some weeks. It may be relieved by the traditional medicaments (ointments, suppositories, and antihistaminics) but it is by no means always controlled. It does not apparently arise as a direct result of gastrointestinal irritation, for it is not necessarily associated with diarrhoea, but seems rather to result from the suppression of organisms in the bowel. It is not related to vitamin-B deficiency, for it is not cured with this vitamin. It is thought to be due to yeast-like organisms, which were found in the rectal smears of 2 patients. Yogurt is being tried in the treatment of this condition in an attempt to introduce more organisms into the bowel. —(Yogurt resembles 'Dahi').

D. D. VORA.

EXTRACT OF LIQORICE FOR TREATMENT OF ADDISON'S DISEASE. Groen, J., Pelser, H., Willbrands, A. F. and Kamminga, C. E.: New Eng. J. Med., 244: 471, 1951.

Borst recently demonstrated that glycyrrhiza extract causes sodium retention and potassium loss leading to an increase in the extracellular fluid, plasma volume, venous pressure, and pulse pressure. He concluded that glycyrrhiza contains a substance with desoxycorticosterone-like action. Groen and his co-workers administered 15 Gm. of glycyrrhiza extract per day to a patient with Addison's disease previously controlled with desoxycorticosterone acetate. Mineral equilibrium was maintained as long as the glycyrrhiza therapy was continued. Withdrawal of the extract was followed by reappearance of the clinical, biochemical, and hemodynamic disturbances. A second course of 30 Gm. daily again produced clinical and laboratory remission. In another patient with Addison's disease a crude extract of one of the main ingredients of the extracts, ammonium glycyrrhizinate (3.3. Gm. daily orally), maintained sodium, potassium, and chloride equilibrium. Glycyrrhizonic acid is a component of the glucuronic acid and glycyrrhetinic acid. The latter is a polyterpen with a structural formula exhibiting a striking resemblance to the cyclopenteno-phenanthrene steroids, to which group desoxycorticosterone belongs.

D. D. VORA.

JUDGMENT ON A.C.T.H., Annotations, British Medical Journal, 2 : 785, 1951.

The suppression of active rheumatoid arthritis by A.C.T.H., has ceased to be a dramatic experiment and become a recognised therapy. Adequate dosage at the earliest possible moment in the acute case gives the best results. After the initial response, maintenance therapy must be employed to prevent relapse. For this the repeated injection of A.C.T.H. has not the convenience of oral cortisone. But if cortisone is given for a long time it may be wise to maintain adrenal activity by repeated short courses of A.C.T.H. The superiority of A.C.T.H. over salicylate therapy in rheumatic fever has yet not been decisively proved, and prevention of permanent cardiac damage must be the criterion on which it is judged. In diffuse collagen disease the fundamental question is whether or not suppression of symptoms and signs is accompanied by alteration in the natural history of the disease. Renal lesions in disseminated lupus erythematosus have failed to respond to A.C.T.H. despite considerable improvement in the skin lesions and decrease in constitutional disturbance. The creatinuria of this disease is not abolished. This shows that basic disease process goes on along its natural course while A.C.T.H. removes the usual clinical signs. Because the effect of A.C.T.H. is thus temporary rather than permanent it is most valuable in self-limiting conditions such as status asthmaticus. Decisive relief here is usually obtained by A.C.T.H., especially given intravenously, when other remedies have failed. The results of A.C.T.H. therapy in blood diseases have been disappointing. Gluco-corticoids cause the disappearance of lymphoid tissue, but they do not alter the natural history of lymphoid reticulosis. Anaphylactoid purpura has failed to respond to the hormone. It is useful in the treatment of Simmonds's disease, where the clinical response is excellent and the dangerous tendency to hypoglycaemia is abolished.

D. D. VORA.

TREATMENT OF THYROTOXICOSIS WITH 2-CARBETHOXYTHIO-L-METHYL-GLYOXALINE (C. G. I), Lawson, A., and Berry, G. : Lancet, 2 : 621, 1951.

The daily dose of the drug is 10 mg. Observations were done on 14 patients. The basal metabolic rate and plasma cholesterol level were done weekly; differential white cell counts were done on alternate days and in few cases tracer doses of radioactive iodine were given at the beginning and end of the treatment. There were 11 cases of primary and 2 cases of secondary thyrotoxicosis and one of recurrent thyrotoxicosis. Besides clinical improvement, there was diminution in the basal metabolic rate which usually fell after 3—5 weeks. In a few cases there was gain in weight. The pulse did not decrease remarkably. There was no increase in the size of the thyroid nor its vascularity, and there was no discomfort in the neck. There was occasional leucopenia which responded to treatment with vitamin $B\text{-}_6$. It was used by the authors for getting the patient fit for the operation, or as the only form of treatment. When used alone the same dose was used to maintain the progress. Operation was resorted to in six cases after a preliminary course lasting 3—5 weeks. At the operation the thyroids were neither hard, friable, nor highly vascular, as is generally after the thiouracil therapy. Thus it is a drug effective in small doses, it rapidly improves the general condition, and renders the operation possible after a short period of treatment.

D. D. VORA.

CALCIFEROL, STREPTOMYCIN, AND PARA-AMINOSALICYLIC ACID IN PULMONARY TUBERCULOSIS, Fielding, J., and Maloney, J. J. : Lancet, 2 : 614-617, 1951.

In the treatment of lupus vulgaris, the response to the treatment with massive doses of calciferol occurs in two phases. First, a short phase lasting two to three weeks, during which the disease is activated. This has been referred to as early "Herxheimer-like" reaction, and is compared to a focal tuberculin reaction. Histologically, there is a sarcoid reaction with increased vascularity during this phase. During the second phase, which begins in about 5—6 weeks, there is healing of the lesions, which on histological examination shows histocytic and fibroblastic infiltration, causing a progressive "strangulation" of the tuberculous processes by young connective tissue. The authors utilized the first phase in bringing about a close and intimate contact of the streptomycin in inaccessible pulmonary lesions like cavitation, wherein the results of streptomycin treatment are poor. This type of lesion does not respond to the streptomycin because of low concentration of the drug in the lesion, which besides giving a poor response is responsible for the emergence of resistant strain of organisms. Para-aminosalicylic acid was added, for its property of diminishing the rate of streptomycin-resistant strains of organism produced during the streptomycin treatment.

Calciferol alone exacerbates pulmonary tuberculosis because the initial phase of response of exudative reaction might prove dangerous because of hemoptosis in unsupported lung tissue, and the possibility of bronchial spread. During this phase chemotherapy given seems to control the infection.

The authors chose those cases of pulmonary tuberculosis in which cavitation was conspicuous radiologically. The following course was adopted. Streptomycin hydrochloride was given 0.5 Gm. twice a day ; sodium P. A. S. was given 4 Gm. four times a day ; calciferol 600,000 units in oil once a week intramuscularly for three doses, followed by two doses at fortnightly intervals, and a further 600,000 units every 4 weeks until nine doses had been given—i.e., a total of 5,400,000 units in about 5—6 months. The principle followed was that where marked activity of the disease was shown by pyrexia, streptomycin and P. A. S. were given first and calciferol added shortly afterwards ; where there was little or no pyrexia, all three drugs were started together. Of the six cases treated on the schedule above, three received full course of calciferol with concurrent P. A. S. and streptomycin for 4—6 months, and showed a remarkable degree of resolution and contraction of the infiltrative lesions. The cavitation which was a feature in these cases was not demonstrated by radiography at the end of this course, and did not reappear after 12, 15 and 18 months. Two patients received calciferol for only 1 and 2 months respectively ; both showed a reappearance of the cavitation associated with the induction of pneumoperitoneum shortly after the cavities had collapsed. Two patients showed no response to a first 8 weeks course of streptomycin and P. A. S. whereas a second course of the same combined with calciferol resulted in a rapid diminution in cavity size. In one case, an interval of 2 months separated the courses. In one case the patient was treated with calciferol while her strain of tubercle bacilli was resistant to streptomycin. She deteriorated.

D. D. VORA.

The chances that a forthcoming blessed event will produce twins are one in 92. Triplets are born once in 9400 confinements, and quadruplets once in 620,000 confinements. The likelihood of quintuplets is extremely remote and that they will live even more so. The chances of a multiple birth are shown to increase progressively with the advance in age of the mother to a maximum at ages 35-39. The probability is about 17 in 1000 for women in their late thirties, as contrasted with only 6 in 1000 for teenage mothers.

—Quoted from American Practitioner 2 : 724, 1951.

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ORIGINAL ARTICLE

MODE OF ACTION OF VITAMIN D

ITS EFFECT ON THE CALCIFYING CAPACITY OF RACHITIC EPIPHYSES

P. K. Dikshit * and V. N. Patwardhan *

The role of vitamin D in the cure and prevention of rickets has been known for a fairly long time and yet the exact mechanism by which this vitamin manifests its action is not fully understood. At one time it was believed that it acted mainly through increasing the absorption of calcium and/or phosphorus from the intestine. Laskowski[10] (1937) and Dols *et al.*[4] (1937) have shown that phosphorus absorption was not effected by vitamin D. Nicolaysen[14] (1937) found that in rachitic rats the absorption of calcium from the intestine was higher than in rats protected by vitamin D. On the other hand, Patwardhan and Chitre[17] (1942) observed that vitamin D did not directly influence the absorption of calcium from the intestine of albino rats. Although it is true that there occurs a shift of calcium from faeces to urine under the influence of vitamin D, unequivocal proof that it is specifically the absorption of calcium that is affected is still lacking (Wolbach,[26] 1947).

That vitamin D administration influences blood plasma composition in such a way as to make the fluid environment favourable for bone formation, has been shown by many workers (Rapoport and Guest,[20] 1938 ; Freeman and McLean[5], 1941 ; and Patwardhan, *et al.*[18], [19] 1944, 1945). Dikshit and Patwardhan[2] (1946) observed the close correspondence between the development of rickets and the state of undersaturation of plasma with respect to $Ca_3(PO_4)_2$ and $CaHPO_4$ and reversal to the state of saturation with the onset of healing under the influence of vitamin D. The composition of the environmental fluid thus plays a significant part in determining the calcification of the rachitic bones, *in vivo* and *in vitro*. It has been reported that rachitic bone slices could calcify when immersed in inorganic solutions of suitable calcium and phosphorus concentrations or even in serum obtained from normal animals (Shipley, Kramer and Howland,[24] 1926).

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It is inconceivable that vitamin D acts on the bone merely by increasing the concentration of calcium and phosphorus in the serum. According to Nicolaysen and Jansen[15] (1939), increasing the concentration of calcium and inorganic phosphorus by subcutaneous injections did not lead to normal bone formation in rachitic animals in the absence of vitamin D. Further, the fact that administration of massive doses of vitamin D results in demineralization of bones as reported by various workers (Brown and Shohl[1], 1930 ; Harris and Innes[6], 1931; Patwardhan and Chitre[16], 1938), lands support to the suggestion that the mode of action of vitamin D may be other than increasing the absorption of calcium and/or phosphorus from the gut or increasing the concentrations of these elements in blood.

That vitamin D had no 'local' action on the rachitic bones was first reported by Robison and Rosenheim[21] (1934). These workers did not find any beneficial effect of vitamin D in the *in vitro* calcification of tibial bone slices from rachitic rats. Venar and Todd[25] (1934), however, have reported that an aqueous medium containing vitamin D did have some beneficial effect on the *in vitro* calcification of rachitic bones.

In view of the above, it was considered necessary to reinvestigate the possibility of the existence of a local action by vitamin D in the *in vitro* studies and secondly to obtain, what may be called, direct evidence for its systemic action with particular reference to the calcification of bone.

EXPERIMENTAL

Young rats, four to five weeks old, were fed the Schneider and Steenbock[23] (1939) rachitogenic diet modified by Dikshit and Patwardhan[3] (1947) having a Ca:P ratio of approximately 10:1. The diet was given for a period of two weeks during which time, moderately severe rickets developed in all the rats. The animals were killed by stunning and their tibiæ removed under aseptic conditions. The proximal heads of the tibiæ were carefully cut longitudinally and the bone slices obtained were placed in a sterile calcifying medium described by Robison and Rosenheim[21] (1934). This medium contained calcium, inorganic phosphate and organic phosphate in amounts similar to those found in the plasma or serum at a pH between 7.2 and 7.4. Thus a 10 : 4 : 1 calcifying solution contained 10 mg. Ca., 4 mg. inorganic P and 1 mg. organic P (sodium glycerophosphate) per 100 c.c. solution. The tubes containing the bone slices were incubated at 37° C for 19—20 hours. At the end of the incubation period the bone slices were removed, fixed in 10 per cent formalin solution for 2 hours and then washed and stained by von Kossa's silver nitrate method. One slice from each bone was fixed in a 10 per cent formalin solution *immediately after* cutting, *i.e.*, without incubation in the calcifying solution. This is necessary since it helps in ascertaining whether any calcification had taken place *in vivo* before the bones were removed from the body. The extent and intensity of calcification in the rachitic cartilage were recorded according to the method first used by Robison, Macleod and Rosenheim[22] (1930). Thus the maximum marking 10 ≣ indicated "that the new calcification extended throughout the entire area and had a maximum density in the zone of hypertrophic cartilage previously uncalcified."

Effect of addition of vitamin D to the calcifying medium :—Since vitamin D is insoluble in an aqueous medium, it was felt that this fact in itself would make the demonstration of a local action of vitamin D in calcifying solutions a difficult matter. Hence attempts were made in the following manner to incorporate vitamin D in calcifying solutions so that it would be present in a state of fine dispersion.

1. A solution of vitamin D in oil (irradol) (containing 10,000 I.U. vitamin D per Gram) was saponified, and the nonsaponifiable matter was dissolved in propylene glycol—a water miscible substance. Six drops of this propylene glycol solution of vitamin D (containing 1,000 I.U.) were thoroughly mixed with 15–20 cc. of sterile calcifying solution. The control consisted of a calcifying solution containing an identical amount of propylene glycol without vitamin D.

2. The nonsaponifiable matter as obtained in 1, was dissolved in alcohol to give a concentration of 10,000 I.U. of vitamin D in 1.5 cc. of alcoholic solution. 0.1 to 0.2 cc. of this alcoholic solution containing about 700 to 1,400 I.U. of vitamin D were added to 15—20 cc. of the calcifying solution. A calcifying solution containing the same amount of alcohol served as a control.

3. The alcoholic solution of the nonsaponifiable matter, as obtained in 2, was treated with digitonin and the sterols were removed. The sterol-free nonsaponifiable matter thus obtained was redissolved in alcohol and 0.3 cc. of this solution containing approximately 2,000 I.U. of vitamin D was incorporated in the calcifying medium.

4. 0.1 Gm. of the irradol solution was added to 15–20 cc. of the calcifying solution. The emulsion obtained was stabilized with 25 mg. of saponin added to the calcifying medium. Controls with saponin and oil but without vitamin D were kept.

5. An emulsion obtained by mixing 15–20 cc. of the calcifying solution and 5 drops of vitamin D_2 in oil (containing 10,000 I.U. of vitamin D) was stabilized by the addition of 20–30 mg. of lecithin to the medium.

Bone slices obtained from rachitic rats were immersed in the above mentioned solutions and in the corresponding controls. Any difference in the calcification of the bone slices that occurred in the control and experimental solutions could thus be ascribed to vitamin D. In none of the above cases was any beneficial effect of vitamin D observed on the *in vitro* calcification of the rachitic bones. Thus it would be reasonable to conclude that vitamin D has no local action on the bone.

Effect of vitamin D administration to rachitic rats on the calcifying capacity of their bones in vitro :—It has been observed by many workers that there is a time lag between the administration of vitamin D and the first evidence of its action on rachitic epiphyses. The possible reasons which can be advanced by way of an explanation are that either (a) vitamin D on entering the body sets in train certain alterations in the structure and metabolism of rachitic caritlage before it is ready to calcify, or, (b) the vitamin itself undergoes some change in its structure or state of combination before it can exert its typical action. It is possible that delay in the manifestation of vitamin D action in bone may be the resultant of both these factors.

In a young rat suffering from vitamin D deficiency the epiphyseal cartilage becomes hypertrophic. There is no transition from the normal cartilage to degenerated and calcified cartilage, hence the normal sequence of calcification is held in abeyance. After the administration of vitamin D this sequence seems to be re-established by the formation of a provisional zone of calcification proximal to the hypertrophic cartilage zone. It may be argued that the events leading to the formation of a provisional zone of calcification may probably take some time and it is this step that is responsible for the time lag between the administration of vitamin D and its action which first becomes manifest in the provisional zone of calcification.

The fact that vitamin D by itself fails to show a local effect on the *in vitro* calcification might also lead to the suggestion that probably the vitamin is first converted to an active substance in the body before it can exert its action. Vitamin D may enter into combination with a protein carrier, which could then bring about the well known effect of vitamin D action. Analogous behaviour can be cited in the case of vitamins like vitamin A and several members of the B complex. The fact that no such compound of vitamin D has been isolated is no proof that such a combination might not occur.

It was considered desirable first to explore the possibility of demonstrating pre-calcification changes in the rachitic epiphyseal cartilage of rats which had been administered vitamin D. The results obtained are described below.

Rats fed a rachitogenic diet referred to earlier were given various doses of vitamin D orally and then killed at intervals of 24, 48, 72 and 96 hours. The tibial bone slices of each rat were treated as follows. Two slices from each of the two tibiæ were fixed directly in 10 per cent

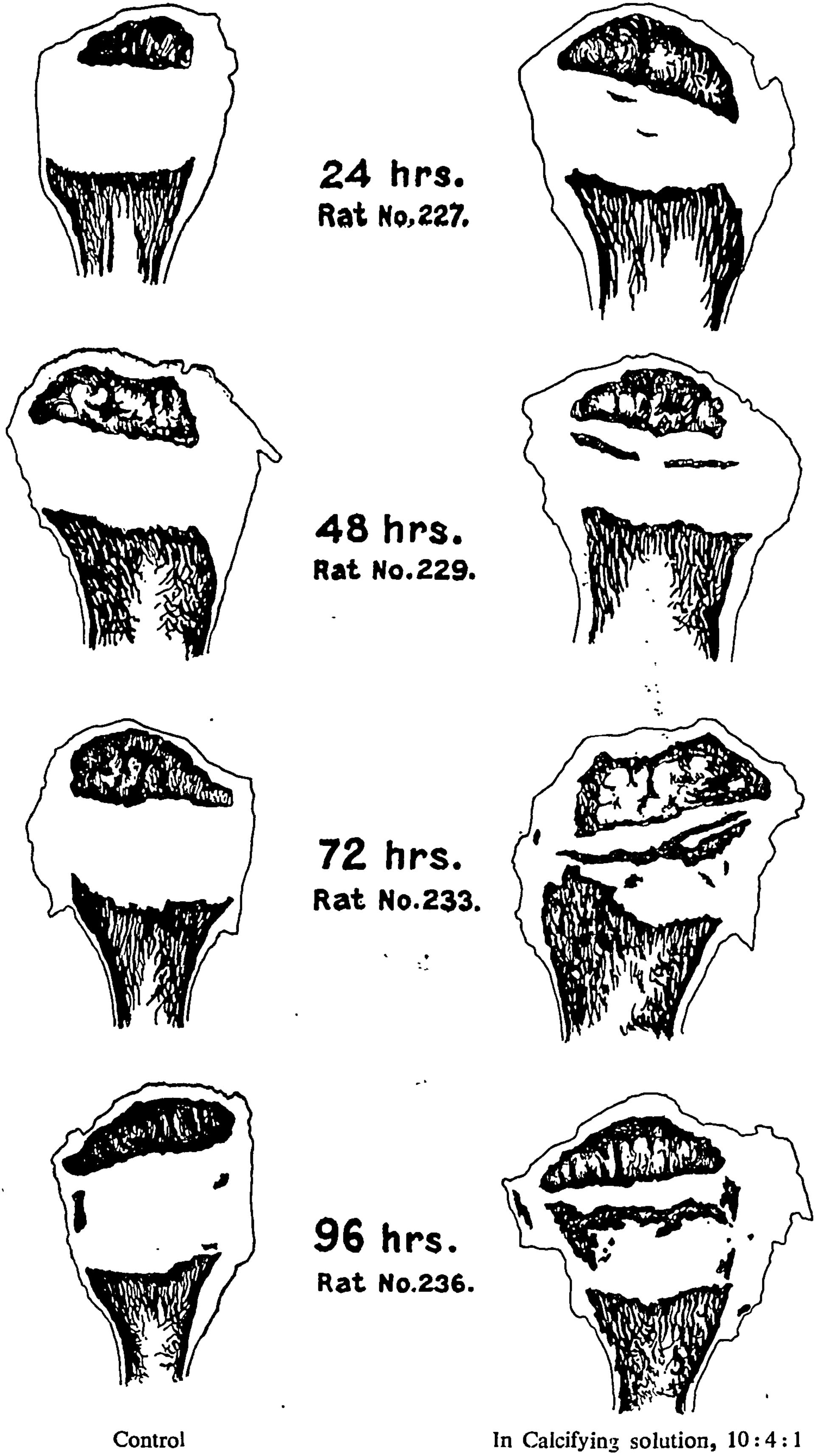

Fig. 1.—Calcification in rat tibiae. Rachitic rats-administered vitamin D. 4000 I.U.

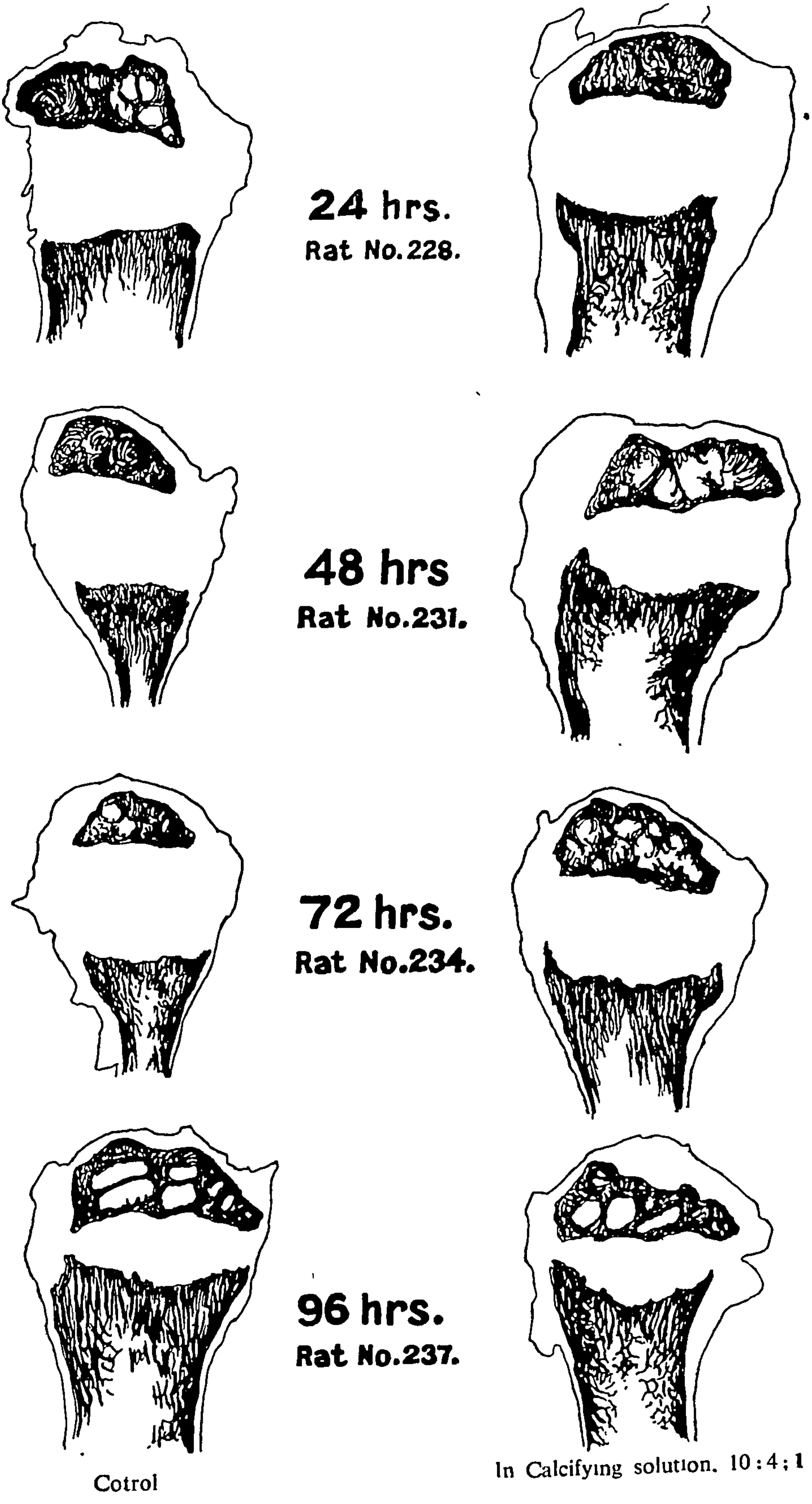

Fig.2.—Calcification in rat tibiae. Rachitic rats-no vitamin D administered.

formalin, the remainder were transferred aseptically to sterile calcifying solutions, incubated at 37° C for 19-20 hours and then fixed in formalin. Both sets were then stained by von Kossa's method. Slices from control rachitic rats which had not received any vitamin D were treated in an exactly similar manner.

As a result of a few preliminary experiments it was found that rachitic bone slices would show little or no calcification in calcifying solutions 9 : 5 : 1, 10 : 4 : 1 or 10 : 5 : 1 (Ca : inorg. P : organic P); these concentrations were, therefore, used in the present experimental study. Further, it was observed that an oral dose of 4,000 I.U. of vitamin D gave reproducible results at various stages. In the experiments described below the above standard dose had been administered. The results of a typical experiment are illustrated in figures 1 and 2.

It will be clear from the figures that on administration of 4,000 I.U. of vitamin D orally the first evidence of calcification *in vivo* in the provisional zone becomes evident only after 96 hours, for all the slices of bones, obtained from animals between 25 and 72 hours after vitamin D administration and directly fixed in formalin, failed to show the occurrence of any calcification. On the other hand, when slices obtained from the same bones were incubated in calcifying solutions, they showed an increasing capacity for calcification with the increase in the interval after vitamin D administration (See Fig. 1). Thus 24 hours after vitamin D administration, the *in vitro* calcifying capacity of the bone slices was least, but it appeared to increase, till after 96 hours it was almost maximum. It was at this time that the beginning of calcification *in vivo* first became apparent (See column 10, Table 1). The graded increase in the calcification seen in Figure 1 is significant in the light of the above observation. In Figure 2 are illustrated the results of similar treatment of bone slices from rachitic rats, not given vitamin D. At no stage was there any evidence of calcification either *in vivo* or *in vitro*. In Table 1, the results obtained in a few other experiments are given for purposes of comparison.

DISCUSSION

The experiments reported here confirm the observations of Robison and Rosenheim [21] (*loc. cit*) that vitamin D has no direct or local action on the bones. On the other hand, they have furnished cogent evidence concerning the systemic action of vitamin D. By this action, vitamin D appears to influence the mineralization or calcification of the rachitic bones in a medium which otherwise does not promote its calcification. Further, these studies clearly indicate that the action of vitamin D on bone is distinct from its effect which results in an increase in the concentration of calcium and phosphorus in blood. The possibility that both these actions might be inter-related cannot, however, be ignored.

TABLE 1. *Experimental Results of in vitro Calcification of Rachitic Bones.*

Expt. No.	Calcifying solution	*In vitro* calcification of rachitic bones obtained from animals administered 4,000 I.U. vitamin D. Animals sacrificed at stated intervals after vitamin D administration.							
		24 hours		48 hours		72 hours		96 hours	
		In calcifying solution.	Control.	In calcifying solution.	Control.	In calcifying solution.	Control.	In calcifying solution.	Control.
1	I 10 : 4 : 1	(i) 0.1	0	0.8	0	4	0	4	0.3
		(ii) 0.2	0	0.0	0	2	0	3	0.0
	10 : 5 : 1	(i) 0.5	0	0.8	0	4	0	4	0.3
		(ii) 0.3	0	1.0	0	3	0	4	0.0
2	9 : 5 : 1	..	..	0.0	0	2	0	5	0 (?)
3	9 : 5 : 1	..	..	2.5	0	3	0	4	0.5
4	9 : 5 - 1	0.1	0	1.0	0	2.5	0	7	1

(N. B.).—There was absolutely no *in vitro* or *in vivo* calcification in rachitic bones obtained from animals not administered vitamin D but sacrificed at corresponding intervals.

The above statement, that vitamin D exerts a positive effect on calcification of the bone, is in conflict with the view expressed by Migicovsky and Emslie[11], [12] (1947, 1949). These workers expressed the opinion that vitamin D acted on the bone, resisting the solvent effect of an adverse mineral equilibrium which exists in a rachitic animal. They have further stated (1950) on the basis of their studies on the deposition of radioactive calcium administered, both orally and intramuscularly, to rachitic chicks and to those which had been administered vitamin D that this vitamin did not cause any direct mineralization of the bone, but that it helped in the greater retention of the bone minerals.

It is not intended to refute the suggestion that vitamin D may also act on the bone in such a way as to enable it to resist dissolution. However, on the basis of the results obtained in the present study, it is maintained that the increased calcification *in vitro* of the bone slices of rachitic animals, which were previously fed vitamin D, could not be solely ascribed to a favourable environment resulting from an increase in the calcium and/or phosphorus content of the environmental fluid, since the concentrations of Ca : inorg. P : org. P in the experimental fluid were maintained at a constant level throughout. It seems that due to the action of vitamin D, the bones were in a state favourable for the deposition of minerals from the environmental fluid. In this connection, a reference to the work of Kraemer, Landtman and Simola [9] (1940) may not be out of place. These workers observed that the bones of rats receiving large doses of vitamin D took up relatively more calcium from a solution containing calcium and also gave up less calcium to a calcium-free solution than the bones of vitamin D deficient rats, which took up less calcium from the medium and also gave up more calcium to the calcium-free solution.

It is difficult to visualize, at the moment, the procedure by which vitamin D on administration imparts an enhanced calcifying capacity to rachitic bone which can be demonstrated by *in vitro* calcification experiments. Any suggestion that may be put forward at this juncture must necessarily be in the realm of speculation for want of more specific information. However, it seems likely that vitamin D might act on the hypertrophic cartilage cells either by bringing about some change in them or in the inter-cartilaginous matrix. Some clue to the change that may possibly occur in the cell due to the presence of vitamin D may be obtained from Kodicek's work on bacteria. Kodicek [7] (1949) has reported that the long chain unsaturated fatty acids like oleic, linoleic and linolenic acids exert a bacteriostatic effect on the growth of a number of gram positive bacteria, *viz., L. casei, L. arabinosus, Str. faecalis, and E. coli, etc.* The bacteriostatic action was reversed by some surface active agents among which vitamins D_2 and D_3 were quite important. Kodicek[8] (1951) has observed with the help of electron microscopy that linoleic acid causes certain alterations in the cell membrane of the bacteria whose growth was adversely affected. The structure of the cell membrane was restored to normal by the substances which reversed the inhibitory action of linoleic acid. In the light of this report it is considered possible that the effect of vitamin D deficiency could be a derangement of the metabolism of the epiphyseal cartilage and/or an alteration in the structure of the cell membranes of the cartilage cells and the osteoblasts or of the matrix elaborated by them which seems to be unable to take up the mineral salts in vitamin D deficiency. The wide osteoid border, characteristic of rickets, should bear evidence that such is in fact the case.

It will be interesting to find out in what way the metabolism of the epiphyseal cartilage cell is affected under the influence of vitamin D. Further, the influence of vitamin D on the cell membranes of cartilage cells and osteoblasts should deserve closer attention, for it is felt that alterations in the structure of these cell membranes may themselves profoundly affect the metabolism of this tissue. One thing, however, is clear, that it is not so much the environment as the structure and metabolic activity of the cartilage or osteoid that may determine whether calcium salts are deposited or not. Further work on these interesting points is in progress.

SUMMARY

1. An investigation on the mechanism of vitamin D action was carried out by experiments on the *in vitro* calcification of rachitic rat bone slices.

2. Vitamin D incorporated in calcifying media in a fairly dispersed condition showed no 'local' action on the bones.

3. Rachitic bones from animals previously administered with vitamin D, but not exhibiting any *in vivo* calcification, showed much greater calcification *in vitro* than the bones of animals not given vitamin D.

4. The *in vitro* calcifying capacity of the rachitic bones appeared to increase with the increase in the time between vitamin D administration and killing of the animal followed by removal of the bone. The maximum calcifying capacity *in vitro* coincided with the first evidence of calcification having commenced *in vivo*.

5. The implications of these observations are discussed. It is suggested that calcification depends not so much on the composition of the surrounding medium as on the state of the cartilage cell and matrix Vitamin D probably influences either the metabolism or structure of the epiphyseal cartilage cell and osteoblasts and the relative matrices rendering them capable of laying down the bone salt.

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One of us (P. K. Dikshit) wishes to express his grateful thanks to the Raptakos Medical Research Board, Bombay, 18, for the award of a Fellowship which enabled him to take part in this work.

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ULTIMATE VALUES

SAVONAROLA, (1452-1498), "Medical World," **74** : 467, 1951.

The physician that bringeth love and charity to the sick, if he be good and kind and learned and skilful, none can be better than he. Love teacheth him everything, and will be the measure and rule of all the measures and rules of medicine.

NEPHROPEXY—THE "CURE ALL", PROFESSOR CHARLES A. PANNETT: St. Mary's Hospital Gazette, Medical World, **74** : 433, 1951.

Let me give you an illustrative example of the surgery which mechanistic views and practical surgeons led to. In my early days the fixation of the kidney was one of the commonest procedures to appear on the operation list. The "floating" kidney was blamed, not only for pains in the back, but for a large number of apparently remote complaints. By dragging on the duodenum it caused indigestion. by pulling on the common bile-duct, jaundice and gallstones, on the colon it caused colitis. Its effects, far from being confined to the abdomen extended right up into the midbrain and cerebrum. The harassed housewife, ill-adjusted in her arduous struggle with domestic problems, was to be cured by preventing the drag on the renal plexus and the far-reaching effects of this disturbance of the sympathetic system. Even mental disease was to be cured by nephropexy. This is no exaggerated picture of the mass influence of a few enthusiastic surgical cranks. What a prolific field for surgical enterprise! One cynic said that there was not a woman living within twenty miles of a midland town who had not had her kidney stitched to her last rib.

ORIGINAL ARTICLE

THE ROLE OF AYURVEDIC MEDICINES IN THE TREATMENT OF DIABETES MELLITUS †

S. S. Ajgaonkar *

My interest in diabetes dates back to 1932 when my uncle who suffered from diabetic gangrene of the lung went from bad to worse with the allopathic treatment available. This led me to a study of Ayurvedic literature from which I evolved a method of treatment which worked a marvellous cure and so stimulated me to set it down so that others may benefit.

My researches on the value of a high carbohydrate, low fat diet interested Prof. Porges in Vienna when the Nazi regime brought our work to a standstill. On my return from Europe, my work interested Dr. M. D. D. Gilder, the Hon. Health Minister in 1947, who was good enough to allow me to carry out further investigations at the Sir J. J. Hospital under Dr. R. V. Sathe. The present paper is based on the cases treated at the Sir J. J. Hospital with a modified scheme of treatment in a period of a year and a half with the addition of some cases from my private practice.

Diabetes mellitus was known to our forefathers over 2,000 years ago, who described the symptoms accurately :

"Burning of the palms, of the soles ; heaviness of the body, urine sweet and white, drowsiness, thirst and malodourous breath. While a diabetic who has been affected with boils and carbuncles and with other complications should be considered incurable, and the diabetic can be considered as cured when the urine is clear, tastes aromatic and there is no albumen and sugar [1,17,19]."

They thought that metabolic diseases, if not treated properly, would turn into diabetes mellitus after some time and thereafter become incurable. They also knew that there are two types of diabetes—congenital and acquired ; the former they predicted as incurable while the latter as curable. They were of the opinion that the congenital manifestations needed a nourishing diet while the acquired ones needed restriction.

The credit for discovering sugar in urine is given to the English physician, Dr. Thomas Willys, but this fact was definitely known to our great savants of Indian medicine much before, but their treatment was not on satisfactory lines. In later years, both dietetic treatment and physical exercises were included in the treatment of diabetes but still very negligible progress was made till minerals were introduced in the therapy of the disease. Charak[1] and Sushrut [17]used decoctions of herbal drugs and shilajit predominantly. The later physicians, Nagarajun, Yashodhar[15] and others, used minerals in the form of different Bhasmas along with the herbal remedies. There is many a formula in different ayurvedic books. The following minerals are particularly recommended by various ayurvedic authors of old for diabetes and urinary disease as a whole:—

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† Paper read before the Eighth Bombay Medical Congress on 26-11-1950.

* Department of Medicine, Sir J. J. Hospital.

Jasad Bhasma—a preparation of zinc prepared according to ayurvedic process.
Nag Bhasma—a preparation of lead.
Wang Bhasma—a preparation of tin.
Shilajit

I noted that these basic drugs did not solve the problem. Besides, Nag, *i.e.*, lead was considered as a poison in modern medicine. So I had to evolve my own formula, taking into consideration the bio-chemical and pathological aspect of diabetes. Before I discuss my line of treatment it would not be out of place if I give a short sketch of the present day conception of diabetes and its treatment with its advantages and shortcomings.

The modern concept of diabetes started with the presence of sugar in urine in the year 1654 by the English physician, Thomas Willys. Thereafter, different laboratory methods of examination of urine for sugar, acetone bodies, *etc.*, and so also the blood sugar curves, added to our knowledge of the chemical pathology of diabetes.

The experiments and studies of Claude Bernard, Von Mehring, Minkowsky and others directed attention to the importance of the pancreas in the metabolism of carbohydrates and fats. It was noted by different physiologists that the beta cells in the pancreas (islets of Langerhans) when healthy, prevented diabetes even though two-thirds of the pancreas was removed. The credit goes to Prof. Banting and to Best who worked in co-operation with Prof. McCleod to discover insulin, thus opening a new era.

Insulin was hailed as a life-saving remedy and we admit it is definitely so in juvenile cases. It helped the diabetic to take a liberal diet and the old regime of starvation became a part of history. During infection especially, it is a life saving drug, and deaths from coma have been on the wane. With wider use, one came across cases resistant to it, where the dose had to be increased steadily and still the diabetes could not be brought under complete control. It is reported that the normal secretion of insulin in man is 40 units or more, but we come across cases in need of over 250 units daily and, in some cases, over 850 units a day are required [20]. Recently, a case has been reported where a patient required

16,050 units of insulin in 24 hours. It was observed that two cases with the same percentages of sugar in the urine required different doses—one under 20 units and the other 80 units or over. Why is this so? It is obvious that there must be some anti-insulinogenic factors working against the normal secretion of the pancreas and thus causing a deficiency.

During infection, mental strain, emotional stress, *etc.*, we observe that the insulin requirement is increased. From all these factors, it will be seen that diabetes is a more complex phenomenon than just a disease of the pancreas.

I believe that as glycosuria is a symptom, as fever is a symptom, there must be many factors in the causation of diabetes. We find glycosuria and hyperglycemia under following conditions :—

a. diabetes mellitus
b. thyrotoxicosis
c. pregnancy
d. infections and toxemias
e. liver diseases
f. pituitary and adrenal diseases.

Glycosuria is merely a reflection of an imbalance of the endocrine system. The fact is now appreciated that the disease need not be of pancreatic origin. Hyperfunction of the pituitary and the adrenals can as possibly produce abnormalities of carbohydrate metabolism as can hypo-function of the pancreas. This explains the cases where no pathological changes of the pancreas are seen in some diabetics or cases where no relationship exists between the degree of pathological changes in the islets of Langerhans and the severity of the diseases. The newer knowledge re-emphasizes the necessity for individual therapy in the treatment of diabetes and that insulin is not the end at all. Two individuals showing equally severe abnormalities in carbohydrate metabolism vary widely in their usual requirement of insulin because the origin of their symptoms may be in the abnormal functions of different glands[6].

How can we overcome the disadvantages of insulin—its careful regulation requirements, the dangers of hypoglycemia, its tendency to lead to obesity, and the bogey of disuse atrophy of the islets of Langerhans and chronic insulin poisoning?

Laboratory work has convinced Somogyi that in most diabetics the liver cannot metabolise the fats fast enough. Physicians working with him in St. Louis reject the common idea that the patient's intake of starches must be restricted, instead, they make the patient cut down on fats to ease the load on the liver and to get his weight down to the ideal norm for his age and height [13].

The pancreas must be made to secrete its own secretion according to the need of the body even if the other endocrine organs are acting at variance with it, and we must counteract their influence and thus save the pancreas from exhaustion and degeneration.

Faulty diet has been condemned as the cause of diabetes. An excess of carbohydrates in the diet is supposed to be the cause, but if one goes through the statistics of different nations one will be surprised to find that Japan whose staple food is rich in rice and fish, has the least number of diabetics, while America and other countries have the most [2,10]. Then one finds remarks that diabetes is a disease of the rich with sedentary habits. Though its percentage is more in the rich and obese, as these approach the doctor early, it is also seen among the poor and undernourished. One cannot explain juvenile diabetes on this theory alone. The patients that attend the diabetic clinic at the J. J. Hospital come from the poor and lower middle class and live on a mixed diet, like the Christians and Mohammedans ; a very few are vegetarians and Hindus. It must be considered a constitutional disease, hereditary, in the majority of cases. Julius Baur has said "As far as the pathogenesis is concerned, it has always been my belief that diabetes mellitus cannot be considered a disease merely of the Langerhans' islets of the pancreas. The other endocrine glands such as the pituitary, adrenals and indirectly the thyroid, parathyroids and gonads are involved in the regulatory mechanism of carbohydrate metabolism. The autonomic nervous system and the liver are of equal importance in this respect. The nervous system not only regulates the function of the endocrine glands and the proper liberation of the respective hormones at the proper time but takes a direct part in regulating hepatic glycogenolysis[11]. Soskin speaks of diabetes mellitus as a syndrome and not as a disease, the various links in metabolic changes having only a different share in the pathogenesis of diabetes. The modern trend to consider it an endocrine imbalance opens new vistas of research. The recent experiment of Houssay, Young and others, of injecting pituitary extracts in a dog and so producing artificial diabetes, supports the same view. It will be noted that Charak and Sushrut [1,17] the early pioneers of ayurvedic medicines considered diabetes mellitus as an end result of disturbed metabolism.

It was believed that diabetes could not be cured but it is now known that after proper treatment the pancreas shows signs of regeneration in the islets of Langerhans. Boyd [3] has reported a case of a diabetic boy, killed accidentally, in whom there was a regeneration of the cells of islets of Langerhans. Joslin and John [8,10] have quoted Lukens and Dohan who say that there are two stages in the pancreas of a case of diabetes. Stage I is reversible, where there is swelling of islets of Langerhans and vacuolation or loss of granulation of these cells. Stage II is irreversible where there is hyaline degeneration leading to fibrosis and destruction. Moreover, nature has endowed the pancreas with an ample functional reserve for any emergency. Joslin says that one tenth of the pancreas is sufficient to prevent diabetes.

Taking all these points into consideration we come to the conclusion that though diabetes is a disease of insulin deficiency, there are one or more factors at work, such as :—

(*a*) deficient secretion by the islets of Langerhans of pancreas,
(*b*) the action of the anti-insulinogenic function of the pituitary, thyroid, adrenals and other endocrine glands,
(*c*) impairment of the action of insulin due to the disturbance of the functional capacity of the liver,
(*d*) infections and toxemias giving rise to insulin anti-bodies and anti-hormones,
(*e*) the action of the vagus which may alter the functions of the pancreas and the liver,
(*f*) the kidney which may have some unexplained part in the syndrome as can be seen from the coincident high blood pressure,
(*g*) the acceleration of the destruction or elimination of insulin and
(*h*) the blockage of the access of insulin to the body cells.

All these may, therefore. cause disturbances in the carbohydrate metabolism in particular, and the fat and protein metabolism in general, producing hyperglycemia and acidosis. According to Peters and Vanslyke[18], the characteristic metabolic defect is the rate of combustion of carbohydrates which is persistently incapable of acceleration to the maximum that it can attain in the normal subject.

PHARMACOLOGICAL ASPECT OF THE AYURVEDIC DRUGS USED

I have based my new line of treatment considering diabetes as a syndrome and attacking all the aspects of its causation. While referring to the ayurvedic treatment of diabetes, I mentioned certain Bhasmas especially Jasad, *i.e.*, zinc. It is interesting to note that of all the organs in the body, the highest amount of zinc is found in the pancreas. It has been suggested that insulin is stored in the pancreas, as a zinc complex. Scott and Fisher[10] found after analysis of the normal and diabetic pancreas that whereas there was on the average 1.7 units of insulin per gram of non-diabetic pancreas, the corresponding value of the diabetic pancreas was less than 0.4 units. A similar difference was noted with regard to the zinc content of the pancreas, there being 0.14 mg. of zinc per gram of normal pancreas, as compared with 0.07 mg. of zinc per gram in the diabetic pancreas. So zinc must have something to do with the nutrition of the pancreas and also the secretion of insulin. The metal is seemingly an essential element in the nutrition and growth of the animal kingdom[16]. It is also an important constituent of the red blood corpuscles. Experiments with zinc free diets plus vitamins by Bertrand and Bhattacharji[14] led to death in mice, while the addition of zinc had beneficial effects. Recent work has shown that 22 micrograms of zinc per day caused a 50 per cent decrease in growth and delay in intestinal absorption. Because pituitary transplants caused amelioration of the condition, it was suggested that zinc is necessary for the formation or utilisation of one of the pituitary hormones. It has also been suggested that zinc acts as a catalyst. That zinc is connected with oxidation and reduction in cells was the conclusion reached by Reed and Dufrenoy[18] from a study of citras leaves suffering from a deficiency of zinc. Zinc is probably an indispensable element like magnesium, iron, *etc.*, Till now zinc has been used therapeutically, only externally, but has not been used orally or parenterally except in combination with insulin as protamine zinc insulin, and that too recently. Many will be surprised to note that zinc in the form of Jasad Bhasma was used for over 1,000 years along with other medicines for diabetes mellitus, orally, by our Indian physicians. Until recent years, the part played by traces of zinc, cobalt, flourin in human nutrition has been somewhat neglected, because in man, clear-cut evidence of deficiency states, attributable to a deficiency of these elements, is rare. With the demonstration that cobalt is an essential component of the vitamin B_{12} molecule, this field of nutrition is rapidly gaining importance[21]. Our forefathers in medicine, without the help of laboratories, inferred that zinc was a drug of choice in diabetes. Perhaps, zinc may be working on the defective pancreas to stimulate or regenerate the islets of Langerhans or, as mentioned above, zinc may be necessary for the formation or utilisation of one of the pituitary hormones controlling the pancreas. If some biochemist finds out an easy test for zinc excretion in urine and we test diabetic and non-diabetic urine, we may get further data. Normally 0.3 mg. to 0.6 mg. of zinc are excreted in the urine per day[16]. Tracer elements, like radioactive phosphorus and iodine, may show the way they act on any organ. So if one made zinc radioactive, and traced its progress in the body, one may find the seat of its action.

The idea that the nervous system is the only means of control in the organism has been relinquished and the importance of chemical co-relation is now generally recognised. Each hormone exerts its effects to some extent on all the organs and tissues of the body. From all this it will be seen that chemical stimuli through minerals have some important function in our body metabolism. I have used metal Bhasmas on my diabetic patients and I will now discuss some of the important ones used in the present investigation (diabetic patients, treated at J. J. Hospital since 1-8-1948 and which are under my observation).

Jasad Bhasma :—We have discussed the pharmacology of zinc and it will be observed that zinc is an important element in the body metabolism and especially in that of the pancreas and the pituitary. In Rasachandrika, Jasad has been described as useful in diabetes, anemia, *etc.*, It seems likely that it acts on the endocrine glands like the pituitary and the pancreas. It is said that it is specially useful in the thin type of diabetic patients[5].

Wang Bhasma or Stannum :—This is a preparation of tin and has been used for diabetes for over 1,000 years. It acts on the lymphatic system and on the kidneys. It is also useful in staphylococcal infections. Recently, it was used for enteric fever. It removes (diminishes) albumin in urine. It is also used as a stimulant to the gonads by the ayurvedic physicians in the form of Suwarnaraj-Wangeshwar[5].

Nag Bhasma :—This is considered as one of the main drugs in the therapy of diabetes mellitus especially in obese types[14]. It is said to reduce sugar both in the blood and urine. It is used as a tonic. There is no clear indication of its seat of action[5].

Abhrak Bhasma :—This is supposed to replace the diseased tissues and help to regenerate healthy normal tissue in diseased organs. It also acts as a sedative to the higher nervous centres in the brain according to the ayurvedic books[5].

The other drugs like prawal, shilajit, *etc.*, are complementary to the above drugs. It will be noted that certain metals have been in use for many years both in ayurved and modern science. Some of the drugs mentioned are not yet used internally in modern therapy, while they were so used by the ayurvedic physicians for over 1,000 years. It is feared that lead (Naga) if taken internally may cause lead poisoning. But Nag Bhasma prepared according to the special process of ayurveda does not show any untoward effect both clinically or on blood examination. All the patients taking the above drug were examined frequently, hematologically, and no abnormal changes were found.

PROCEDURE FOLLOWED IN THE INVESTIGATION OF THE DIABETIC PATIENTS

Before proceeding to give the results of the above medicines on diabetic patients treated during the last year, it is necessary that I should explain the manner of investigation and the treatment followed in the cases reported.

1. Every patient was examined according to a performa appended. The history was taken, diet was recorded and the blood sugar curve was taken on the diet which he was used to, with or without insulin, as the case may be. A 24 hour urine sample was tested. The insulin dose if any was noted and the patient was asked to attend every week for further observation with a 24 hours sample of urine for further tests. A week or two was allowed without medicine. A balanced diet was prescribed if the usual intake of the patient was defective. Usually, 200/250 grams of carbohydrate which with other food stuffs produced 2000/2400 calories, were prescribed to an adult taking into considera-

tion the optimum weight and height of the individual and the work he did. It will be noted that the dietary requirements of people in the tropics are definitely lower than those in the temperate climates[4]. The diet was adapted to the tropical requirements.

2. Diabetic tablets prepared with zinc, stannum, calcium, iron and a trace of Nag (lead), *etc.*, were given to the patients in doses of from 3 to 6 tablets a day according to the needs.
3. If the patient was taking insulin previously it was continued for some time in the same dose and was slowly reduced as the sugar in the urine got less and less and finally insulin was stopped.
4. If the patient was a rice eater, it was not prohibited. It may be mentioned that 100 Gm. (3-1/2oz.) of rice contained 78/79 Gm. of carbohydrate, while wheat flour contained 74/76 Gm. per100 Gm. Rice was restricted to the quantity allowed.
5. Weight and blood pressure and urine examinations were recorded every week. Blood sugar examinations, both fasting and with breakfast, were frequently done, as also the blood examinations of the erythocytes and leucocytes. (total counts, differential counts, hemoglobin, *etc.*)

RESULTS

In the majority of patients, the fasting blood sugar and even sugar after breakfast came down to within normal limits. The 24 hours sample of urine was sugar free in 28 cases, and their general condition improved immensely. All the symptoms subsided. No insulin was given to these patients even though they were taking it before the present treatment.

In 16 cases, the patients' urine sugar was less than 1 per cent. These cases are needle free, *i.e.*, without insulin and on a liberal diet as can be seen from their increase in weight. One case, even though with a tubercular focus and who once had hemoptysis for over 8 months, showed 0.5 to 1 per cent of sugar. When he came to us, he was passing 4 per cent sugar with a blood sugar curve at 356 mg. per cent—445 mg. per cent—448 mg. per cent—468 mg. per cent—361 mg. per cent. His fasting blood sugar taken last was 120 mg. per cent with a diet containing over 300 grams of carbohydrates and of a caloric value of 2,700.

Many other patients, who attended the hospital and were taking insulin for months together before they came under my observation, are now needle free and some are completely free from sugar in urine for months together. Over 25 cases which were examined and treated till now with this new oral treatment have left Bombay and so could not be followed. Only those cases that were followed for a period of over three months are taken into consideration. It will be seen that those cases which attended the diabetic clinic regularly have definitely benefited by the treatment. Some patients, of course, did not react. It may be that like insulin cases, they are resistant to treatment. Some of the patients, once free from sugar in the urine, after the treatment do not attend the clinic for regular observation even though letters are sent to them, and as such, much of the clinical work is lost.

It will be seen that the following beneficial results have been observed with the new oral treatment of diabetes.

1. there is a definite reduction in sugar both in urine and blood even though the diet is near normal or more. The carbohydrate intake has been more than 200 Gm. in all cases and in some cases more than 300 Gm. Some patients were initially on a less poorer diet than the one we prescribed.
2. There is a reduction in the blood pressure both systolic and diastolic in those cases where it was already high.
3. The tendency for frequent colds disappeared in those who used to have them.
4. The tendency to boils and infection in general was reduced in some cases.
5. Some, though not free from sugar in the urine, are free from the needle for months together.

It will be seen that these ayurvedic medicines increase the carbohydrate tolerance by its improved oxidation which is usually affected in a diabetic. Unfortunately, not all cases showed gratifying results. Some were resistant, some relapsed, and some did not come under, even with insulin. Infection was the main cause. Juvenile diabetic patients also showed resistance.

Diabetes mellitus is not a static but a dynamic state which can vary greatly. It is for this reason that individualisation and readjustment from time to time is necessary. No general routine can be followed in all cases. Each case presents an individual problem.

The criterion as to whether the treatment is helping the patient or not should, I think, be based on the general improvement of the health of the patient, improvement in the signs and symptoms, reduction in fasting blood sugar, freedom from sugar in the 24 hour sample, reduction in blood pressure and maintenance of optimum weight. If these criteria are applied to the above treatment, the results of the present treatment with Ayurvedic medicines seem promising as can be seen from the accompanying tables of the cases which are practically treated without the help of insulin.

I do not profess that this line of treatment of mine is a complete one. It just shows a new line of thought and approach and can be improved upon so that we may one day reach the goal,—an oral medicine

TABLE 1.—*Summary of Cases.*

BEFORE TREATMENT.

S.N.	Name.	Age. Sex.	Religion.	Duration of Diabetes.	Wt.	Urine 24 Hr. Oz.	Sugar %	Insulin Dose.	BP	Blood Sugar.
1	M. M. J. ..	55/F	M	5 Y	181	40	3.3	Yes	210/110	170 F
2	L. F. ..	50/F	C	6 Y	135	60	5.0	15+15	190/110	169-300-260-240-180
3	M. U. ..	52/M	M	4 Y	128	36	5.0	No	126/82	128-206-265-178-178
4	F. U. ..	50/F	M	6 M	150	40	1.2	Yes	185/120	206-347-357-348-274
5	R. T. M.	70/M	M	1 Y	132	96	4.0	20+20	185/120	357-445-448-468-361
6	W. M. C.	58/M	M	2 Y	140	40	2.0	20	135/80	195-300-416-396-
7	D. L. C. ..	55/M	C	2 Y	138	40	4.0	40	155/110	203-308-377-358-
8	P. M. R.	48/M	H	1 Y	125	60	2.0	60+20	120/60	153-260-333-353-
9	A.R.A.L.	46/M	M	5 Y	127	48	4.0	20+20		244-270-328-334-392
10	I. S. N. S.	35/M	S	4 Y	128	40	2.35	Yes	100/70	168 F
11	K. H. ..	52/F	M	6 M	123	40	1.0	Nil	160/80	250-280-344-380-380
12	A. ..	60/F	M	1¼ Y	190	80	2.2	Yes	140/90	185-260-306-287-240
13	V. V. ..	47/M	C	4 Y	175	40	1.7	c40PZi	120/70	188-276-488-350-268
14	J. C. ..	57/M	C	3 Y	118	60	2.5	c20+20		258-306-432-456 380
15	T. A. ..	50/F	M	3 Y	115	112	3 to 5	Yes	125/80	Hyperglycemic Curve
16	D. R. S. ..	48/M	H	1 Y	140	46	1.	Nil	140/85	F 161 mg.%
17	J. M. ..	35/F	M	5 Y	140	60	4.0	40+40	125/80	296-347-424-363
18	M. C. ..	38/F	C	1 Y	158	72	1.0	Yes	160/85	Not taken
19	F. C. ..	35/F	C	6 M	112	80	5.0	Yes	130/80	Not taken

TABLE 1.—*Contd.*

AFTER TREATMENT.

Duration of Treatment	Duration of Observation	Wt.	Urine 24Hr. Oz.	Sugar%	Insulin	BP	Treatment. Diabetic	Blood Sugar mg. %	Remarks
6 M	6 M	180	32	0.33-Nil	Nil	180 90	3 Tabs.		No change in diet.
6 M	3 Y	133	80	Nil	Nil	145 80	„ „	F 110	Was operated for carbuncles before treatment. Normal diet. No tables 2 Y
6 M	1 Y	128	36	Nil	Nil	110 70	„ „		Relapsed once but yielded to treatment in 2 months.
6 M	6 M	149	48	Nil	Nil	160 80	„ „		No change in diet.
11 M	11 M	140	64	0.33-Nil	Nil	140 75	„ „	F. 122	T.B. Lungs, Pt. not traced.
3 M	3 M	143	64	0.4	Nil	135 80	„ „	F. 138	Pt. not traced.
4 M	2 Y	144	40	Nil	Nil	140 80	„ „	F. 111	Sugar free for over two years. Does attend the hospital.
5 M	8 M	126	60	Nil	Nil	120 60	„ „	117 B.F.	Full diet Carbohydrates over 300 Gm.
1½ Y	2 Y	134	48	0.5 to Nil	Nil	130 80	„ „	F. 117.6	No change in diet. Blood Sugar 19-10-51, 117.6-217.4-222.4.
7 M	1 Y	128	40	Trace-Nil	Nil	100 70	„ „	F. 120	Blood curve-120-142-200-187. Diet same as before treatment.
5 M	5 M	126	20	Nil	Nil		„ „	B.F. 150	Blood sugar after break fast (B.F.) 150. Pt. Not traced.
3 M	2 Y	180	80	Nil	Nil		„ „		Diet same as before treatment.
1½ Y	2 Y	162	35	Nil	Nil	120 78	„ „	148 after full meal	1½ Hr. Fasting 89.
1 Y	1 Y	112	45	0.5 to Nil	Nil	140 90	„ „	F. 144	Still under observation. 122-164.5-211.2-317.6-287.6 on 30-10-51.
7 M	2 Y	116	48	Nil	Nil		„ „	F. 98	Now takes full diet.
3 M	8 M	136	45	Nil	Nil		„ „		Diet same as before.
8 M	10 M	140	40	Nil	Nil		„ „	F. 162	Takes usual diet.
3 M	3 M	160	30	Nil	Nil		„ „		No change in diet.
3 M	9 M	122	64	1.0	Nil	130 90	„ „		No change in diet. Anæmia

TABLE 1.—*Contd.*

BEFORE TREATMENT.

S.N.	Name.	Age. Sex.	Religion.	Duration of Diabetes.	Wt.	Urine 24 Hr. Oz.	Sugar %	Insulin Dose.	BP	Blood Sugar.
20	K. F. ..	54/M	C	6 M	140	48	2.0		120/70	
21	S. K. ..	51/F	H	3 M	134	30	4.7	40+20	135/80	252-298-398
22	M. ..	46/M	J	3 Y	172	88	4.0	No	135/78	236-334-378-308
23	L. D. G.	52/F	H	6 M	150	56	4.0	20+20	120/80	298-334-350-400 370
24	N. B. P. ..	47/M	H	2 Y	158	60	1.0			
25	L. R. N.	59/M	H	12 Y	158	165	0.9		170/100	F. 230
26	S. P. ..	50/F	H	15 Y	122	30	1.0	20+20	146/80	106-212-279-331 285
27	R. G. B.	45/M	H	1 Y	154	80	1.66	20+20	120/80	195-237-272-295 260
28	H. V. ..	40/M	H	4 Y	137	41	2.0		115/80	220-254-350-296 240
29	T. B. S. ..	45/M	H	1 Y	147	124	1.0	20+20	115/80	
30	I. A. ..	47/M	C	6 M	120	60	2.5	?	160/90	
31	S. M. P. ..	39/M	M	1 Y	130	65	0.5	Nil	125/80	
32	S. M. ..	48/M	C	4 M	155	54	1.5	Nil		
33	N. S. S. ..	57/M	P	1 Y	147	40	2.0	20+20	125/75	
34	J. C. ..	49/M	C	6 M	190	108	0.7	Nil	180/106	
35	S. N. N. ..	36/M	H	8 Y	102	96	2.5	20+20	165/90	
36	L. H. ..	45/F	H	2 Y	106	44	2.5	40+40	135/90	
37	G. Z. ..	50/F	H	8 Y	110	44	4.5	40+40	170/95	
38	S. B. ..	44/F	H	1 Y	126	66	3.3	20+10	110/85	

TABLE 1.—*Contd.*

AFTER TREATMENT.

Duration of Treatment	Duration of Observation	Wt.	Urine 24Hr. Oz.	Sugar %	Insulin	BP	Treatment. Diabetic	Blood Sugar mg.%	Remarks
5 M	6 M	138	38	Nil	Nil		3 Tabs.	F. 97	No change in diet.
4 M	6 M	136	28	Nil	Nil	120/75	„ „	F. 106	Skin eruptions disappeared.
3 M	6 M	170	60	Nil	Nil	130/75	„ „	104-133-169-149-124 on 16-8-51.	Diet adjusted.
3 M	6 M	154	70	Nil	Nil	110/70	„ „		Carbohydrates 200, Calories 1700.
3 M	6 M	158	60	Nil	Nil		„ „		"Carbohydrate" tolerance increased.
8 M	1½ Y	158	116	Nil	Nil	140/85	„ „	F. 130	No material change in previous diet.
4 M	1½ Y		60	Nil	Nil		„ „		Diet 284 Carbohydrate, Calories 2064 and no sugar in urine over 1 Y.
4 M	1 Y		60	Nil	Nil		„ „		Diet 241 Calories 1956.
3 M	1 Y	138	35	Trace-Nil	Nil		„ „		Diet 245 Carbohydrates 2015 Calories.
3 M	3 M	146	140	Nil	Nil		„ „		Relapsed after medicine was stopped for 8 months. Came to normal again after taking medicine for two months.
6 M	6 M		37	Nil	Nil	160/90	„ „		
4 M	8 M	132	60	Nil	Nil	125/80	„ „		No change in previous diet.
2 M	2 M	158	37	Nil	Nil		„ „		No change in previous diet.
3 M	6 M	147	40	Nil	Nil				No change in previous diet.
3 M	4 M		64	Nil	Nil	120/80	„ „		No change in previous diet.
4 M	4 M	102	82	0.5	Nil	140/75	„ „		Modified, Pt. is suffering from Chr. nephritis with albuminuria. ++
6 M	1 Y	113	41	0.25	Nil	120/70	„ „		No change in diet.
4 M	8 M	116	64	0.33	Nil	130/80	„ „		Operated for Carbuncle. Diet 220 Carbohydrates. Calories 1911.
10 M	10 M	111	50	Nil	Nil		„ „		Tuberculosis with pleura adhesions.

TABLE 1.—*Contd.*

BEFORE TREATMENT.

S.N.	Name.	Age. Sex.	Religion.	Duration of Diabetes.	Wt.	Urine 24 Hr. Oz.	Sugar %	Insulin Dose.	BP	Blood Sugar.
39	M. B. R.	31/M	H	3 Y	130	75	2.0	48 to 96	125/90	130-220-250-246 210
40	V. R. K.	49/M	H	3 Y	182	82	5.0	40 PZi	124/80	
41	G. B. K.	52/F	H	10 Y	154	70	2.5	80+80	150-220/120	F. 301
42	K. K. P.	45/M	H	5 Y	135	96	6.6	Nil	135/82	
43	L. L. ..	46/M	C	1 Y	123	160	6.6	Nil	130/80	210-307-421-317 307
44	K. K. J.	45/M	H	2 Y	125	29	2.0	Yes	130/90	
45	M. S. B. ..	48/M	H	2 Y	147	48	2.0	Yes	120/85	
46	M. D. S.	40/F	C	5 Y	138	25	1.0	20+20	150/90	
47	D. D. ..	62/F	C	16 Y	102	94	5.0	20+20	120/60	
48	F. D. ..	49/M	C	2½ Y	200	114	2.5	Yes	110/80	
49	U. W. ..	55/M	H	8 Y	136	120	3.3	Yes	165/90	F. 222 mg.
50	J. V. V. ..	52/M	H	12 Y	164		1.	140	150/100	255-325-394-430 360
51	S. D. ..	40/F	H	4 Y	128	114	3.3	40	150/100	F. 266
52	R. M. ..	29/M	P	2 Y	120		2.5	72	120/70	F. 208
53	F. D. ..	40/M	P	15 Y	196	30	1.1	40+40	150/100	
54	M. B. F.	30/M	P	3 Y	120		6.6	80	110/80	
55	A. P. ..	27/F	C	2 Y	92	72	8 to 12	80+100	110/70	340-460-500-530 570
56	M. T. ..	15/M	H	1 Y	79	80	1.5	60+40		107-218-348-400 364
57	P. S. ..	5/M	H	4 M	30	24	2.0	10+5		

TABLE 1.—*Contd.*

AFTER TREATMENT.

Duration of Treatment	Duration of Observation	Wt.	Urine 24Hr.	Sugar %	Insulin	BP	Treatment. Diabetic	Blood Sugar mg. %	Remarks
1 Y	2 Y	132	50	Trace-Nil	Nil	125/90	3 Tabs.		Blood curve-105, 166, 206, 135, 108. No change in diet.
2 Y	2½ Y	180	?	1.0	?		„ „		Sugar free for 2 years, but relapsed recently.
1½ Y	1½ Y		60	Trace-Nil	80	150/90	„ „	F. 145	Diet not changed. Insulin dose reduced by 80 units.
5 M	5 M	143	72	3.3	Nil	135/80	„ „		Diet 229 Carbohydrate, 2541 calories.
4 M	10 M	140	68	0.83	Nil	125/75	„ „	F. 107 after food 210	Used insulin for 15 days, later occasionally, no insulin since Feb. last.
2 M	2 M	125	32	0.33	Nil		„ „		No change in diet. Pt. not traced.
5 M	9 M	155	44	0.50	Nil	120/80	„ „		Diet 125 Carbohydrate, calories 2123.
3 M	3 M	138	40	0.4	Nil	120/80	„ „		Diet no change.
6 M	8 M	106	66	1.66	Nil	105/60	„ „		No change in diet. No medicine for one and half month.
3 M	6 M	204	100	0.33	Nil	110/80	„ „		No change in diet.
3 M	3 M	136	40	1.4	Nil	110/70	„ „		No change in diet. Pt. not traced.
1 Y	1 Y	164	?	0.3	30+80		„ „		Blood cruve-198, 244, 319, 330, 275. Diet not changed.
6 M	6 M	131	96	1.43	Nil	110/70	„ „		Pt. not traced.
1 Y	1 Y	122	?	Trace	20+8		„ „		Pt. was taking 141 Gm. of C. and 2235 calories before treatment. Now taking 220 Gm. C.+2380 calories.
4 M	4M	?	27	0.7	20+40	140/85	„ „		No satisfactory change.
5 M	5 M 2 Y	98	84	2.85	25+40	110/80	„ „		No satisfactory change.
2 Y	2 Y	98	60	2.0	20+30	110/70	„ „		Blood curve 228, 290, 360, 373, 370. No satisfactory change.
2 Y	2 Y	92	80	2.0	30+30		„ „		Did not react satisfactorily
3 M	6 M	33		Trace-Nil	5+5		„ „		Takes insulin on alternate days. Diet :- C-154, Calories 1600.

TABLE 1.—*Contd.*

BEFORE TREATMENT.

S.N.	Name.	Age. Sex.	Religion.	Duration of Diabetes.	Wt.	Urine 24 Hr.	Sugar %	Insulin Dose.	BP	Blood Sugar.
58	E. D. ..	60 M	P	20 Y	170	60	8.0	Yes	130 80	
59	A. R. ..	23 M	M	6 M	104	60-104	3.5-5.0	Yes	120 70	
60	M. T. M.	18 M	H	6 M	77	102-200	5.0-8.0	Yes	110 70	359-383-371-352 348
			ADDENDA:—							
61	A. F. ..	44 M	C	2 M ?	130	30	2.9	Nil		F.280 ; 1Hr.336.2
62	C. P. R. ..	50 M	C	2 M ?	154	36	1.8	Nil		200,210-225
63	D. G. ..	50 M	C	2 Y	130	40	1.8	Nil	130 80	105-251-239
64	I. D. ..	45 M	C	6 M	102	40	1.4	Nil	135 85	212-266-342
65	G. K. ..	54 F	H	10 Y	116	53	5.0	15+25	170 90	
66	H. J. ..	51 M	H	3 Y	143	82	6.6	60+60	110 70	222-341-396
67	S. H. ..	39 F	H	8 Y	118	80	7.7	Yes	120 76	260-286-360
68	K. G. ..	45 F	H	9 M	122	48	3.3	10	140 80	257-327-377-416-344
69	S. M. ..	53 F	H	5 Y	143		5.98	40+40	190 110	
70	G. J. ..	36 M	H	4 Y	166	55	4.0	20	120 70	
71	R. S. ..	55 M	H	4 Y	124	50	4.0	40	150 90	
72	M. T. ..	50 F	P	9 Y	174	82	3.3	Nil	160 110	217-242-280-234

TABLE 1.—*Contd.*

AFTER TREATMENT.

Duration of Treatment	Duration of Observation	Wt.	Urine 24Hr.	Sugar %	Insulin	BP	Treatment.	Blood Sugar mg. %	Remarks
3 M	3 M	172	56	6.0	Nil		3 Tabs.		Discontinued treatment.
4 M	4 M						,, ,,		Pt. did not react.
2 M	2 M						,, ,,		Pt. did not react.
				ADDEN	DA				
3 M	3 M	128	30	Nil	Nil		,, ,,	F.93, 1Hr.-163 2Hr.-101	Diet not changed.
2 M	2 M	152	32	Nil	Nil		,, ,,	F.81, 1Hr. 206 2Hr.-146	Diet as before.
4 M	4 M	132	28	Nil	Nil		,, ,,	F.135, 1Hr.-165 2Hr.-155	
1 M	3 M	102	35	Nil	Nil		,, ,,	F.100, 1Hr.-120 2Hr.-100	
5 M	5 M	112	52	0.5	Nil	146/80	,, ,,		
7 M	7 M	142	56	2.0	Nil		,, ,,		Diet-Carbohydrate 230, Calories 1950.
6 M	6 M	120	46	1.43	Nil	120/75	,, ,,		
3 M	3 M	122	58	0.25	Nil	110/70	,, ,,		Diet not changed.
4 M	6 M	150	24	0.33	Nil	130/90	,, ,,		All symptoms improved.
6 M	6 M			Nil	Nil		,, ,,		Feels perfectly well.
4 M	4 M	123	54	Trace	Nil		, ,,		No tablets taken since middle of May.
4 M	4 M	174	68	Nil	Nil	138/	,, ,,	F. 158 1½hrs. after lunch 174	All symptoms improved.

which will be useful for the majority of diabetics.

There are many secrets which nature will reveal only on painstaking study and observation. Diabetes is such a one. May He show us the light.

SUMMARY

1. A short history of diabetes from Indian and Western medical literature is given.
2. Diabetes a syndrome is discussed.
3. The pharmacology of the ayurvedic mineral drugs is discussed according to both ayurvedic and modern conceptions.
4. Seventy-two cases of diabetes treated with ayurvedic minerals with their results in tabular forms are recorded.

Diabetic patients History and Physical Examination

Month Date M

Year Age F

Name

Address Occupation

Family History and Heredity—

Previous Illness (1) early childhood

(11) adult age :—1 ;	G,	mal.,	dysent.
	pneumonia	sore-throat.	bronchitis.
	typhoid,	rheumatism.	jaundice.

Operations *Habits*—alcohol, tobacco,

Onset of Diabetes & duration.

Constitution— Thin Medium Obese Wt. / Height

Signs and Symptoms—

	Signs		Symptoms
1 Eye—vision	Rt left	other changes	1) Thirst
2 Ears—hearing	Rt left	discharge	2) Appetite
3 Nose			3) Itching
4 Throat—tonsils			4) Burning
5 Tongue			5) Debility
6 Teeth and gums			6) Giddiness
7 Skin—	Anemia		7) Pain & numbness, tingling, etc.
8 Heart blood vessels pulse	B. P.— circulation		8) Mental irritability 9) Dyspnea
9 Lungs	Rt left		10) Cough

10 Liver and Gall bladder
11 Abdomen
12 Pancreas and small intestine
13 Extremities.—neuritis
14 Endocrines
15 Frequency of urine
a) day. b) night.

11) Constipation
or
Diarrhea
12) Sleep
13) Impotence
14)
15)

Urine Report Sp. gr. Sugar, %, Albumen, Acetone, Quantity

1) 24 hour specimen
2) Early morning specimen
3) 3 hours after meals

Blood sugar report & other laboratory findings, etc.

Present diet—24 hours—

Any evidence of septic focus

1) Teeth. 2) Tonsils. 3) Sinuses.
2) Urogenital Tract—Prostate (in men) ; pyelitis, cystitis, F. tubes (in women), cystocele
3) Skin—any abscesses or crop of boils.

Psychic State 1) Equable and phlegmatic or nervous and irritable.
2) any history of psychic shock.

Sexual History.

Endocrine imbalance

General information which the patient need tell the physician.

Remarks by the medical examiner

Medical Examiner.

Diet prescribed and general directions given
Date

ACKNOWLEDGMENT

I take this opportunity of thanking the Hon. Minister for Health, Bombay State, Dr. M. D. D. Gilder, the Superintendent of the J. J. Hospital, Dr. R. V. Sathe, and the post-graduates under him, and Dr. P. V. Gharpure, for the help and co-operation that has been given by them in carrying out this research. I also thank The Indra Laboratories, 127 Bell Lane, Bombay 1, for preparing the Diabetic Tablets according to my formula and supplying the same for this research.

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MEDICAL WORLD, 74 : 551-552, 1951.

'Having Consultant Trouble ?' asks the April issue of Medical Economics, an American monthly journal. From the G. P.'s viewpoint, it appears the that trouble with a consultant is that he may imply that the family doctor has bungled. Now it's hard for the consultant, says M.E., since he's in an awkward position. "If he doesn't alter the treatment, the relatives wonder why they have to pay a large fee for his services, if he does alter the treatment, it looks as if the G. P. has bungled." I agree. It's a hell of a jam. Still, you'll be relieved when you hear the solution. "Successful consultants," the article continues, "work the dilemma out along these lines : if there is medical indication (but not otherwise, of course!) for a change, they talk it over first with the family doctor. They arrange to have the change take effect in a few days. To the family, the consultant then says (hoping, all the time, that he won't forget his lines) : 'Dr. Smith's treatment is exactly what I would have recommended myself. But if the patient doesn't improve by Sunday, we'll use another approach.' This suggests that the family doctor was doing alright, but that the consultant's *visit* was justified in terms of possible future changes. The altered programme, if found necessary, will sound like a co-operative venture between the two doctors."

Well, well! So now we know. It's all rather sordid and just a little shameful. And I know Osler wouldn't approve. One must, of course, be tolerant—after all, they probably felt much the same about taxation without representation. And, perhaps, for all we know, it might be considered un-American for an M. D. to admit that he hadn't a clue and to ask for someone else's advice.

ORIGINAL ARTICLE

OBSERVATIONS ON THE TOXICITY OF WHITE OIL*

R. N. Chaudhuri † and N. K. Chakravarty †

It is now usually held that epidemic dropsy is caused by ingestion of argemone-adulterated mustard oil. This view is supported by epidemiological observations and feeding experiments on human volunteers. Animal experiments were as a rule unsuccessful until last year when an epidemic dropsy-like condition was produced by us in rhesus monkeys with the administration of argemone oil both by the oral route and by injections. Signs of epidemc dropsy, in the form of edema and erythema, were clearly demonstrated. Control animals similarly treated with mustard oil did not show any such change. Argemone oil, when applied to the skin of a monkey produced local erythema and changes in the internal organs showing that the oil is absorbed from the intact healthy skin. All the three argemone-treated animals died of the toxic effects of argemone oil. The histological appearances of the tissues simulated, to a large extent, those of human epidemic dropsy.

In order to find out if there be any other adulterants of edible fats and oils which may be toxic and a contributory factor in the causation of epidemic dropsy, we started tests on monkeys with a very cheap oil *viz.*, mineral oil, commonly known as white oil. It is thin, colourless or faintly yellow, tasteless and odourless, thus having all the requisite qualifications for an adulterant. The details of this experiment in which two different samples of oil were used are given below :—

EXPERIMENTS

Male monkey : weight 6 lbs. diet—normal.

Dose.—White oil (I) 1 cc. per lb. body weight i.e. 6 cc. per day (6 days a week) Total amount—96 cc. in 16 feeds. Weight lost ½ lb after 1st week. In the third week it developed diarrhea and died at the end of the week.

Post Mortem.—Liver—intensely congested. Kidneys—congested. Large intestine—small ulcers. Lungs—congested. Heart—Congested.

The histological appearance in the first animal showed the following features :

Heart.—Dilated blood vessels in between the muscle fibres. Hyalin degeneration of the muscle fibres.

Lungs.—Large congested vessels.

Liver.—Marked dilatation of central veins and sinusoids separating the liver cells.

Spleen.—Splenic sinuses packed with red blood cells.

Large intestine.—Small discrete ulcers, floor formed by submucous coat. Inflammatory reaction, mostly round cells.

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* Paper read at the Annual Conference of the Association of Pathologists of India, at Hyderabad, in November, 1951,

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Stomach and small intestine.—No change.

Adrenal cortex.—Marked engorgement of the capillaries separating the parenchyma cell.

Skin.—Vascular congestion of the dermis.

Kidneys.—A number of dilated blood vessels.

Eye.—Increased vascularity of the choroid layer.

Brain.—No change except some congestion of the meninges.

The histological picture thus appears practically identical with that of argemone-treated animals except for the ulcers in the colon which was possibly due to a terminal superimposed infection.

Subsequently we tested this oil in another monkey :

(2) *Female monkey : weight 9lbs: diet—normal.*

Dose.—White oil (a) ½ cc. per lb. body weight
Total amount 36 cc. in 8 feeds.

The monkey developed a bout of diarrhea and lost 1 1/2 lb. in a week. Died on the 11th day.

In this animal although half the dose (per pound) was used the lethal effect was produced earlier.

Post-Mortem.—Various organs were congested particularly the liver, spleen and the heart.

The histolgocial picture was also exactly of the same nature.

In order to find out whether different batches of white oil are similarly toxic, we tested another sample of white oil on a third monkey :

(3) *Monkey : weight 5 1/2 lbs: diet—normal.*

Dose.—White oil (II) 1/2 cc. per lb. body weight, *i.e.*, 2 1/4 cc. per day—Total 195.35 cc. in three months.

After 3 months : No signs. Weight same. It was killed after 3 months to study the changes.

Post-Mortem.—Liver—congested. Kidneys—slightly congested.

Though it did not develop any sign even in 3 months when it was killed, the histological picture showed a similar type of change but of milder degree.

DISCUSSION

These experiments show the toxic nature of white oil; toxicity varies with different batches of oil. It seems that white oil exerts a poisonous effect on the tissues. The chief action is on the blood vessels, and is of the same nature as that in argemone poisoning in animals. We, however, used in these experiments, the whole undiluted oil in a dose of ½ to 1cc. per lb. corresponding approximately to the daily human consumption of about 2 ounces of cooking oil for each individual in an average household. It has to be seen whether the diluted oil also remains a potent poison.

It is evident from the observations made that the tissue changes of argemone poisoning in animals are probably not specific and may be produced by another cheap adulterant, white oil. From the similarity of the pathological changes, it seems possible that white oil may have some role in the production of epidemic dropsy. Vascular proliferation, however, which is a feature in epidemic dropsy has not been observed in the animals treated with either argemone or white oil.

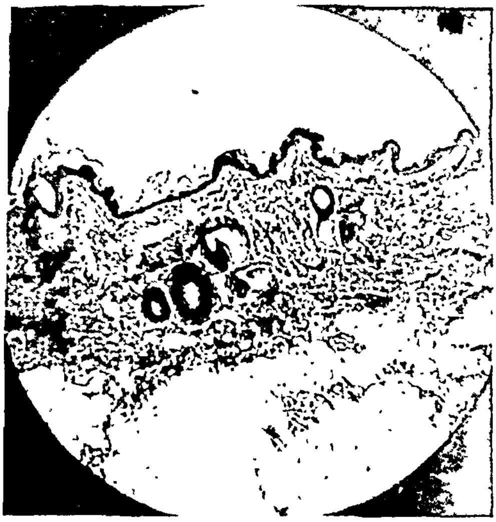


Fig. 1a.—Normal monkey.
(Section of skin).

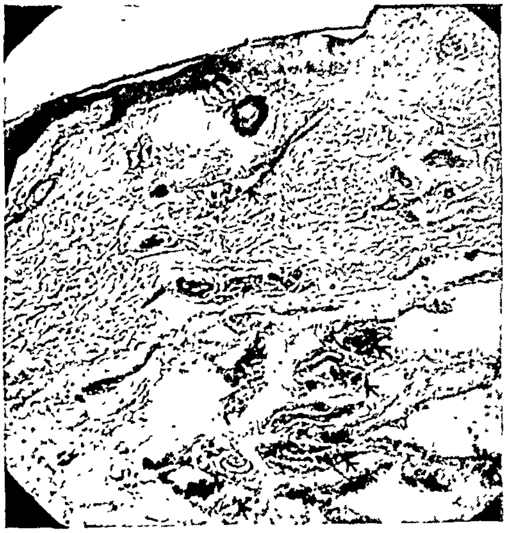


Fig. 1b.—Argemone treated monkey.
(Section of skin).

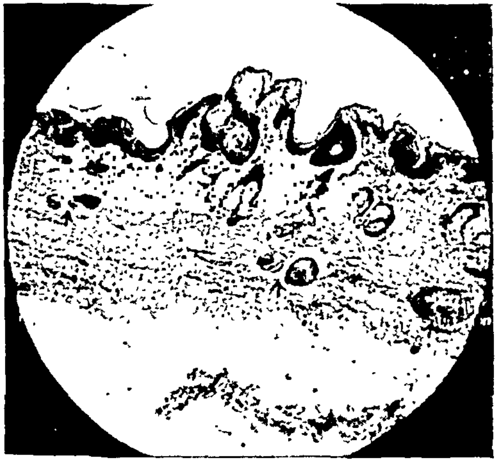


Fig. 1c.—White oil treated monkey. Section of skin showing vascular congestion in the dermis.

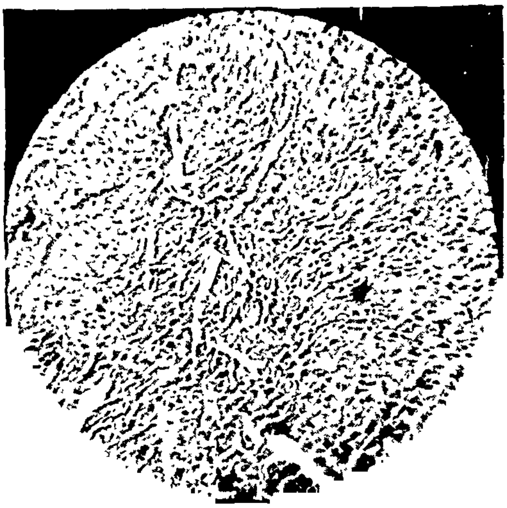
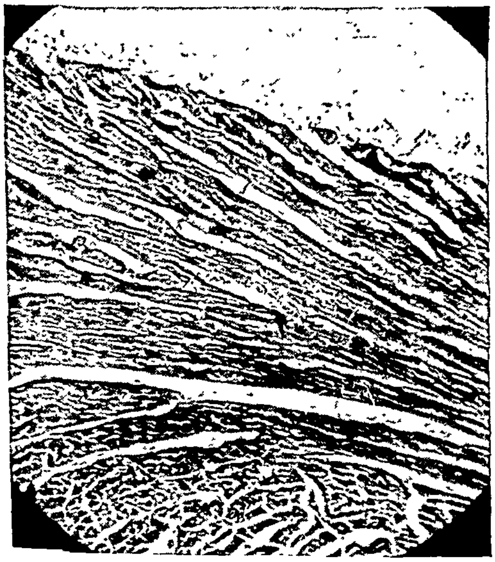


Fig. 2a.—Normal monkey.
(Section of heart).



2b.—Argemone treated monkey.

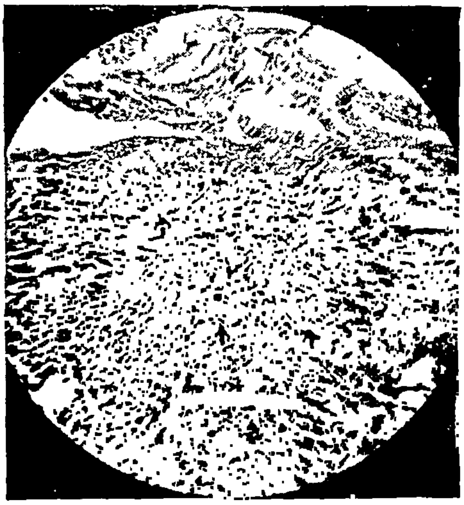


Fig. 2c.—White oil treated mc
Section of heart showing dilated blo

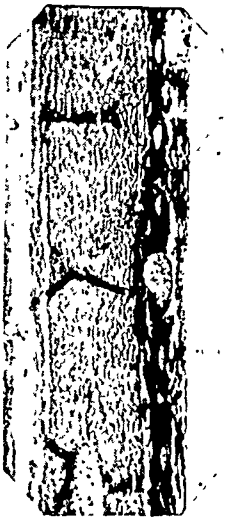


Fig. 3a.—Normal monkey. (Section of eyes).

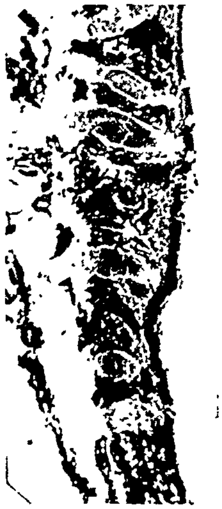


Fig. 3b.—Argemone treated monkey. (Section of eyes).

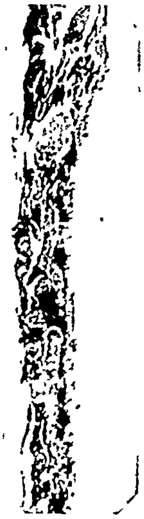


Fig. 3c.—White oil treated monkey. Section of eyes showing increased vascularity of the choroid layer.

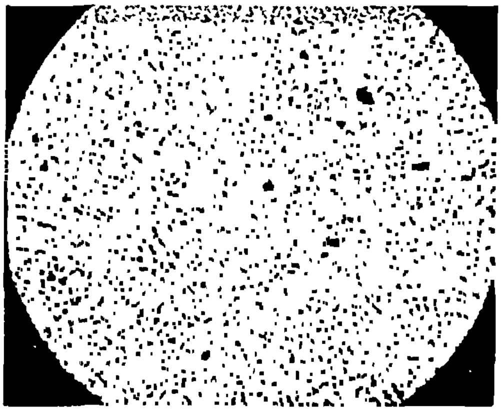


Fig. 4.—White oil treated monkey. Section of liver showing marked dilatation of sinusoids separating liver cells.

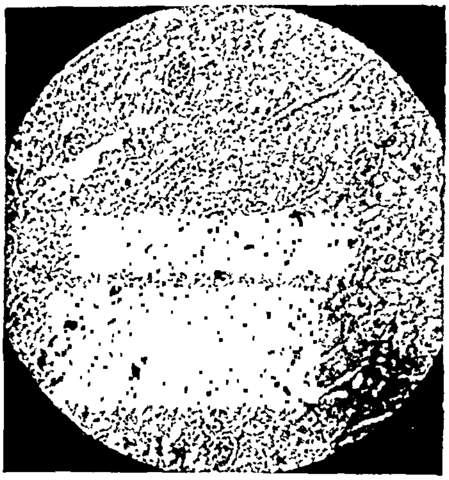


Fig. 5.—White oil treated monkey. Section of kidney showing a number of dilated blood vessels.

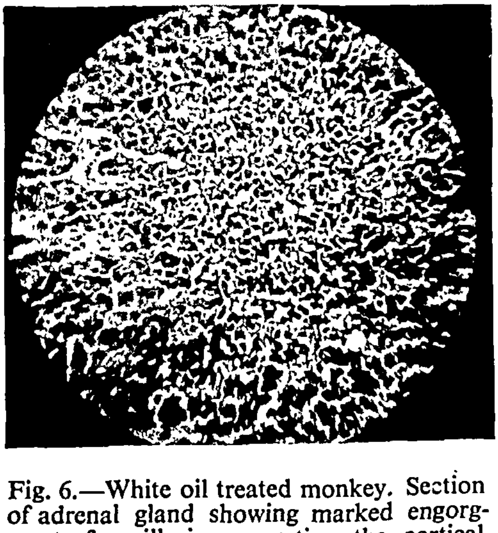


Fig. 6.—White oil treated monkey. Section of adrenal gland showing marked engorgment of capillaries separating the cortical

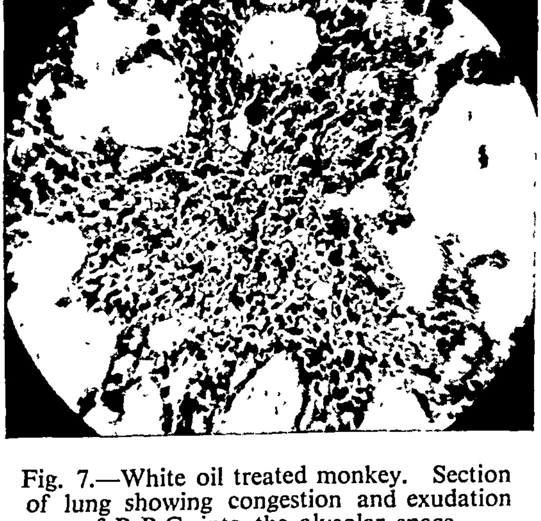


Fig. 7.—White oil treated monkey. Section of lung showing congestion and exudation of R.B.C. into the alveolar space.

In this connection we may add that we have seen a few cases of epidemic dropsy who had not used mustard oil for several months or years. These cases might have been caused by adulteration of other foodstuffs with the argemone seed, as reported in Africa, or possibly, adulteration of cooking fat with a cheap mineral oil, like white oil. This aspect of the problem needs further investigation, and work in this line is in progress.

Ninety-Eight Cents

Somebody has
Taken the trouble
To figure out
What the average person
Has in him
And how much
He is really worth.
First, there is
Water enough
To fill a ten gallon keg ;
The fat would make
Seven cakes of soap ;
Enough carbon is there
For 9,000 pencils ;
And phosphorus
For 2,200 matches.
The manganese would do
For one dose of salts,
And the iron
Could make a little nail.
All the lime needed
To whitewash
A chicken coop
Might be had too.
Last, but not least,
The sulphur
Would just about
Kill the fleas
On one small dog.
These things
Could be bought for
Ninety-eight cents.
With all our skill,
Efficiency,
And economy
Of mass production
There are still
A few tricks
To be learned
From Old Mother Nature.
I, for one,
Am willing to grant
That ninety-eight cents
Might be a low price
For some people.
But there are others
Not worth that much
By far.
Over-production
And depreciation
Are serious problems .
In more ways than one......

—MRS. SMITH

—Tonic and Sedatives, J. A. M. A. 147 : 1951.

My doctor is just back from a convention. He says he's completely prostated.

—Tonics and Sedatives, J. A. M. A, 147: 1951.

Blow Your Top

It once was thought quite declasse
To give vent to one's anger,
And sublimated in that day
Was a pretense of langour.

'Twas thought a virtue, undefined,
To manifest repression
And doctors, too, were of a mind
In this absurd obsession.

The doctor of today well knows
It helps the nervous system
To oft indulge emotions' throes
And not try to resist 'em.

So when you feel you're going to pop
Your buttons, don't ignore it;
Just go ahead and blow your top.
You'll be the better for it.

—Tonics and Sedatives, J. A. M. A, 147 : 1951.

SOME ASPECTS AND EFFECTS OF FAULTY FEEDING IN INDIA

J. P. de Mello*

Malnutrition in India is primarily caused by faulty diet and is not the consequence of repeated famines. Unfortunately, India is a country full of prejudices, with an inherent reaction to changes, specially to its food habits. This has reduced the stature of the average Indian to about 5ft. 3 inches and the weight of an adult to less than 90 lb.

Nutritional deficiency is not only seen among the poor, but is common among those belonging to the higher income group, whose staple diet consists of only cereals and pulses, which have little protein and no fat content. In the average household, milk and ghee are considered as luxuries ; *the latter item of food is expensive as it is used mostly for* religious offerings and lighting funeral pyres, while the former is frequently adulterated and therefore is of limited nutrient value, to substitute the necessary milk for infants fed from stunted and anemic mothers.

From the Municipal Report of Bombay (1949-50), there were 7,458 hawkers importing milk by train. On inspection, 834 were found to have no licenses and 863 were carrying milk in open cans without covers. The number found with grass rings in milk vessels was 95. There are no statistics as to how many samples of milk were found adulterated in this report, but in one place it is mentioned that "out of 28 samples of milk examined at the municipal laboratory, 19 were unfit for human consumption."

The position of a good milk supply is, therefore, a major problem of the city of Bombay and of the health services throughout the country. The Municipality of Bombay, however, has been supplying weak and undernourished children, numbering over 13,000, with about 6 ounces of pasteurised toned milk free of charge, daily, except on Sundays and holidays.

Out of a total of 1,70,002 children in the primary schools of the Bombay Municipality, 20,361 were examined by the medical inspectors in the year 1946-47. Of these, 31.0 per cent had dental defects and 25 per cent suffered from general debility.

The above subject is chosen for this paper because of the writer's recent visit and experience in India, where a state of famine was declared and where the population was undergoing severe food shortages.

The following therefore is the information gathered :

---

* Albert House, Victoria Street, P.O. Box 313, Nairobi, Kenya.

STAPLE FOOD

What is generally known as a balanced diet consists of:

Protein	120 Gm.
Fat	100 Gm.
Carbohydrates	320 Gm.
Water	
Mineral and salts.	
Vitamins.	

Such a balance diet should be able to give 2,500 calories. In India the carbohydrates form the chief item of food and is therefore deficient in the essentials of a balanced diet. The average Indian's food is composed of the following :—

1. Cereals,—rice, wheat, jowar, bajara, maize and barley.
2. Pulses,—gram and dhal.
3. Leafy vegetables,—most of the vegetables are cooked. (No greens).
4. Milk and milk products, such as curds and buttermilk. The fourth item, if used at all as food, is used in very small quantities. As stated before, ghee is hardly used in the average home. For cooking purposes the type of edible oils used are—groundnut, sesame and coconut oils.

In some places, to supplement the acute shortage of cereals,—raji, benti, kodra, samo and wari were used. The flours made from groundnut cake, sweet potatoes, green plantains, yams, rajgira, tapioca and dried pumpkin were also used.

It must be noted that in the majority of the villages of India, the greater bulk of the population is vegetarian and they are accustomed to one type of diet. Food consisting of meat, fish, eggs, fruit, sugar, and jaggery is not in the reach of the average, nor is it desired by the majority as prejudices predominate. It is no wonder, therefore, that deficiency is common even among the well-to-do.

From a series of 335 children examined by Coelho [3] at his consulting rooms the following were graded as :—

Poor	80
Fair	180
Good	75

In this series, the writer does not indicate whether those children were mostly of vegetarian parents, as it would make an important point to assess correct results. Coelho [3] concludes that there is a need of reorientation of food habits,—"We should eat more animal protein and fat and decrease the carbohydrates which to-day supply the bulk of the caloric value. Vegetarianism should be reconsidered till milk and dairy products are made available, in large quantities, to the bulk of the population."

Malnutrition is a serious problem among the children in India.

EFFECTS OF FAMINE

From the superficial survey in famine areas, there were conditions of extreme inanition, crazy-pavement skin and other typical signs of avitaminosis with marked emaciation due to starvation.

Although semi-starved children had signs of edema (some showed typical generalized nutritional edema) there were very few of them with changes in their hair colour from black turning to yellowish or dirty brownish.

The causes of deaths in these areas were due to :—

Diarrheas, dysenteries, edema and respiratory conditions. From records collected during famine in Travancore [10] (1943-44), the causes of deaths were due to :—

1. Edema and dropsy.
2. Diarrhea and dysentery.

In times of famine, gastro-intestinal conditions and edema are the chief causes of deaths. A condition called "Neeru," which means generalized swellings and which is regarded as a fatal signal in famine districts is somewhat analogous with "Kwashiorkor" in Africa.

"Neeru" is caused by hypoproteinemia, with a reversal of the albumin-globulin ratio. Autopsy finding indicates hepatic failure. Neeru is therefore nutritional edema due to a deficiency of proteins in the diet.

KWASHIORKOR

The kwashiorkor syndrome is not an end result of famine in Africa. It is an entity and is occasionally seen only in African children. In East Africa, the tribe that lives only on cereals, like maize, without fresh food, milk, vegetables and dietetic extras, their children are seen suffering from kwashiorkor during the dry season.

Proctor [8] had described it in East Africa as a disease in quite young children, with a fatal prognosis. Cecily Williams [13] described a similar condition in West Africa and called it 'kwashiorkor ; meaning the red boy. Gillan [7] reported a series of cases in Kenya and suggested its relationship to coeliac disease, due to acute diarrhea with fatty stools. Trowell [11] compared the syndrome to one of pellagra.

Scott Brown and Trowell [9] demonstrated in kwashiorkor the deficiency pattern syndrome in the small intestine. Trowell [12] later preferred to call it by the name of "malignant malnutrition." Gillan[7] and Gelfand[6] agreed that it was due to a deficiency of some known or unknown factor. Trowell held the view that the syndrome was a combined deficiency of the vitamin B complex and animal protein and he called it a "pattern of multiple nutritional defects." It resembled Mehlnährschaden (starch or flour dystrophy), as described by Czerny and Keller[4]. This form of dystrophy developed whenever young children are fed on cereals only and where there is deficiency of proteins. Ro

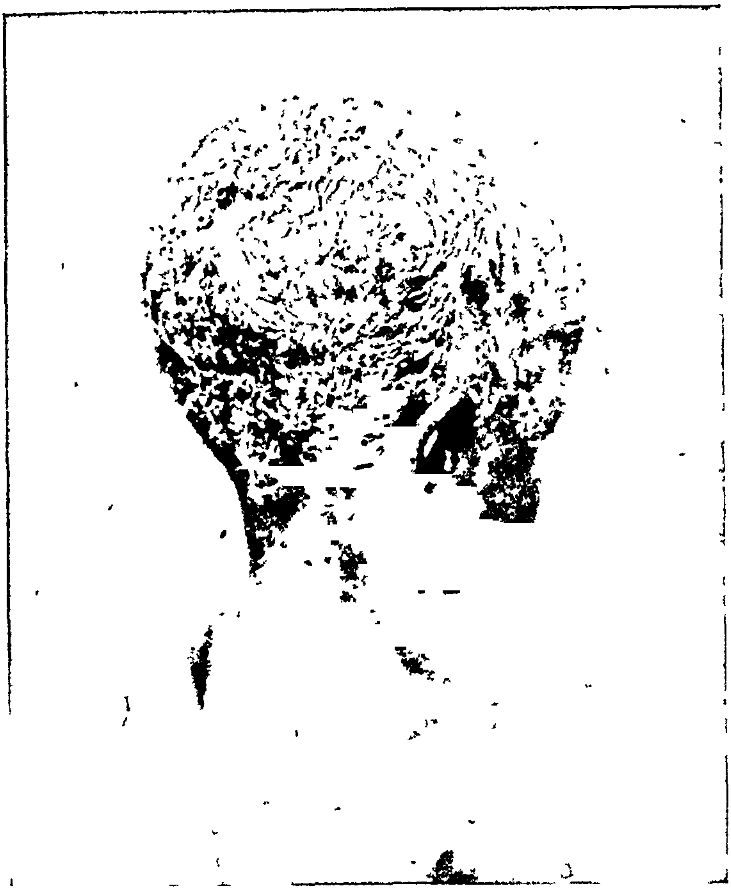


Fig. 1.—Kwashiorkor.—Note the changes in the hair.

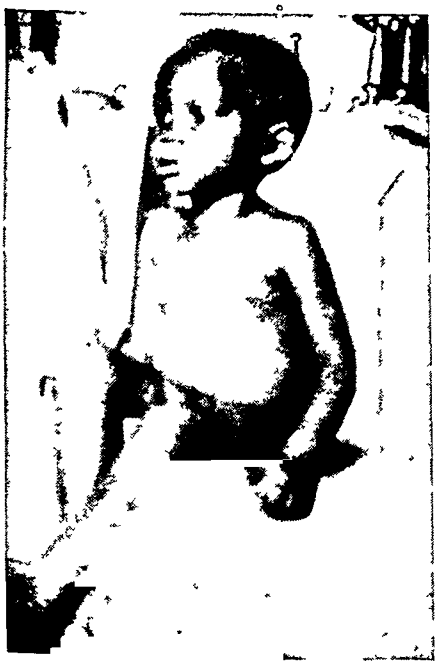


Fig. 2.—Kwashiorkor.—Early case with edema of the legs and early changes

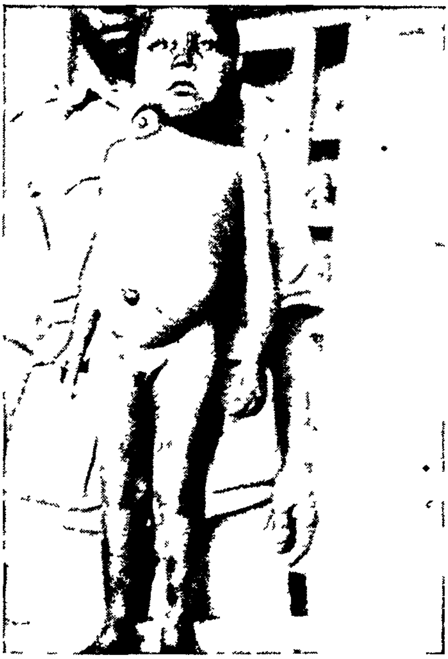


Fig. 3.—Kwashiorkor.—Note the swelling of the face and abdomen.

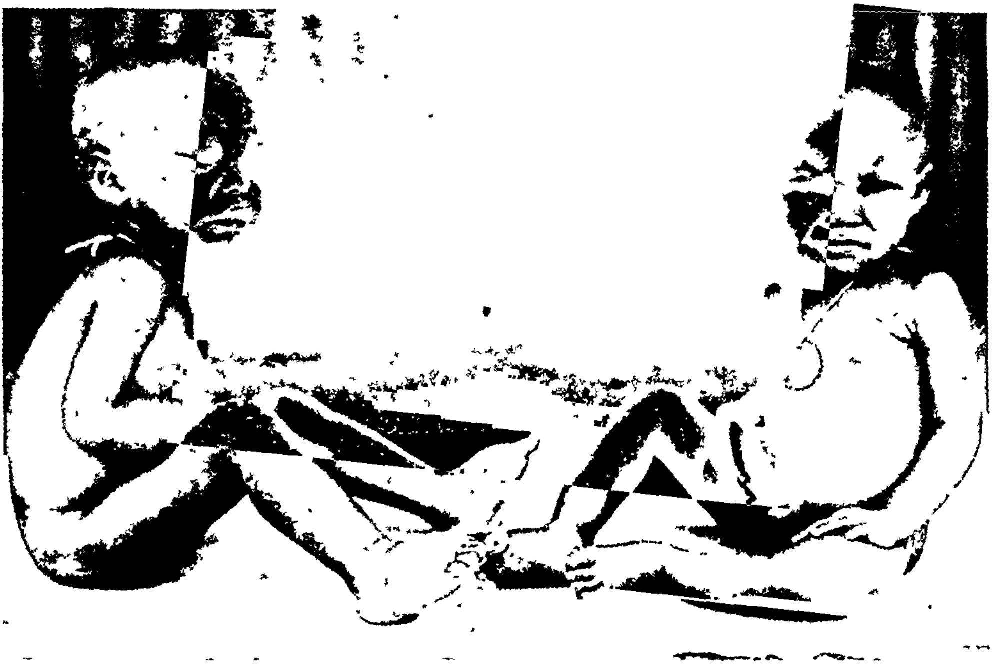


Fig. 4.—Kwashiorkor.

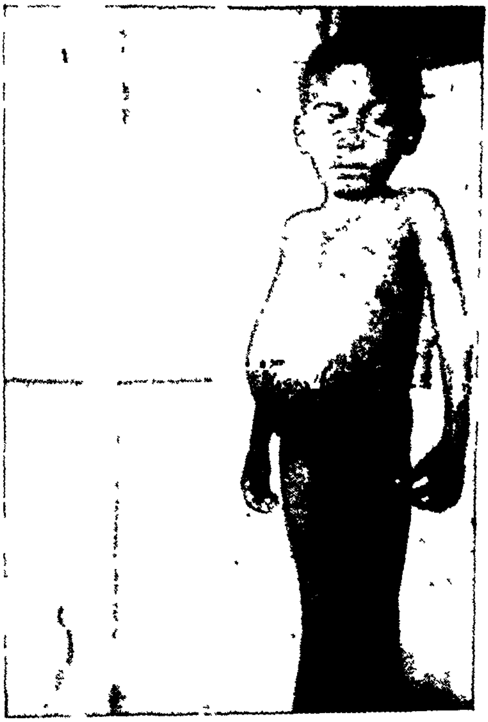


Fig. 5.—Kwashiorkor.—Before treatment.

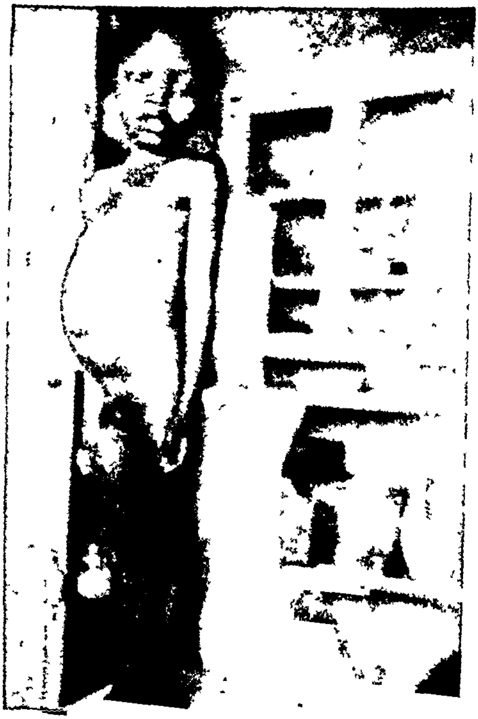


Fig. 6.—Kwashiorkor.—After treatment.

minger [4] pointed out the relationship between Mehlnährschaden and hunger edema, which was seen in starved Chinese children as well.

SIGNS AND SYMPTOMS

1. Skin changes :—From jet black to reddish brown colour. There is a tendency to circumoral depigmentation. Crazy-pavement skin, dermatosis and skin ulceration is frequent.
2. Hair changes :—From curly black hair to reddish tinge, giving the appearance of blonde hair. The hair becomes straight and silky to the touch.
3. Edema :—It is the most serious symptom of the disease. It may be slight, moderate or acute edema. When there is anasarca the prognosis is bad.
4. Diarrhea :—In early cases there is the tendency of loose frothy stools, but in severe conditions, the stools become frequent and are watery.
5. Apathetic :—The appearance of the child is dull and miserable. The child does not show any interest in its surroundings nor does it resist handling during examination.
6. Lack of resistance to cold.

DISCUSSION

It is interesting to observe that there exists a similarity between "kwashiorkor" and the edematous conditions known as "neeru." Fatty infiltration in the liver takes places in both conditions, but that is also found in children dying of tuberculosis or sepsis. Davies [5], however, described in kwashiorkor a significant increase in fibrosis of the pancreas with eventual monolobular cirrhosis of the liver. When this has occurred the liver is damaged for life. In nutritional edema the prognosis is good when the condition is noticed early, and when nutrition is improved, health can be restored. Whereas in kwashiorkor there is a chance of repeated relapses, with stunting of growth, poor physique, poor health and lack of resistance to infection.

Many observers, however, agree that the syndrome of malignant malnutrition conforms with the description of nutritional edema and nutritional hypoproteinemia. In Chinese children suffering from nutritional edema, changes in the hair and skin lesions were seen similar to those seen in malignant malnutrition. In India we were able to record a few cases with discolouration of the hair,—the colour turning from black to yellow or dirty light brown. In some cases, these slightly edematous Indian children showed a reddish-yellow tinged skins.

CONCLUSIONS

1. That certain features of similarity to "kwashiorkor" were seen among the famine cases in India.
2. That the communities of India need a complete change in their general outlook on life and food habits.
3. That malnutrition is common everywhere, even among those belonging to the higher income group, whose food consists of cereals alone.

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Specialization can become confusing to the patient, as witness the man who wrote to a Tulsa doctor.

"Dear Doctor :

When I cough my prostate hurts. Should I see a urologist or a lung specialist?"

JACK SPEARS,
—Tonics and Sedatives. J.A.M.A.

"You say he left no money!"

"No. He lost his health getting wealthy, and then lost his wealth trying to get healthy."

—Tonics and Sedatives. J.A.M.A.

AUREOMYCIN AND STREPTOMYCIN IN OPHTHALMIC PRACTICE

K. Krishna Murty *

AUREOMYCIN

Aureomycin, one of the latest of the antibiotic series, like penicillin, streptomycin and chloromycetin, was one of the best curative antiseptics for the trachoma virus. Reports from the Moorfield Ophthalmic Hospitals and other hospitals on the continent show marked improvement not only in cases of acute conjunctivitis, infective conditions of the eye but also in trachoma of all stages.

Experiments were conducted in the form of an eye ointment and eye drops were used at intervals of two hours for a case of trachoma and the following improvements were noticed.

Trachoma—First Stage :—Redness, photophobia, and watering of the eyes disappear within three days.

Trachoma with Corneal Ulceration :—Ulcers of the cornea begin to heal within three days. The action is hastened if atropine is also instilled.

Trachoma with Corneal Ulceration and Hypopyon :—Frequent application of aureomycin eye ointment will improve the hypopyon within a week, with improvement in the corneal damage.

Trachoma with Pannus :—Aureomycin eye ointment six times a day will improve the pannus within three days. This treatment is by far superior to sulphonamide therapy. Rapid improvement is noticed when sulphonamides are given by mouth and aureomycin locally.

Granular Trachoma :—Granules get flattened with local aureomycin therapy within three days and disappear within ten days. Sulphonamides by mouth hasten the disappearance of granules.

Trachoma—Fourth Stage :—Aureomycin gives definitely good improvement in the fourth stage of trachoma by the disappearance of watering, improvement in vision, *etc.*, Opacities, ectropion, entropion will have to be treated separately.

Acute Conjunctivitis :—Frequent aureomycin drops or aureomycin eye ointment will cure a case of acute conjunctivitis within three days.

Infective Conditions :—Frequent aureomycin drops or 1 per cent eye ointment will improve all infective conditions of the eye such as styes, blepharitis, scleritis, conjunctivitis, iritis, iridocyclitis, and uveitis.

Application of Aureomycin :—There are two types of application ; one in drops and the other in the 1 per cent form of an eye ointment.

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* Department of Ophthalmology, L. N. Hospital, Chodavaram, Vizagapatam District.

The ointment is more convenient to use. Six times a day generally gives quick results.

Treatment of Trachoma :—Duke Elders and his co-workers report a series of eight cases of trachoma treated by one drop of aureomycin at 3 or 4 hourly intervals for ten days with very good results. Though this series is too small to warrant a final conclusion, the therapeutic results are such that the authors believe that "aureomycin will cure the disease in an incredibly short time."

Sorsby advocates a combined therapy consisting of sulphonamides by mouth and aureomycin and mechanical treatment locally.

STREPTOMYCIN

Streptomycin, one of the latest antibiotics, was at first discovered in combating tuberculosis. Its usefulness as an antibiotic in diseases of the eye was recognised by the leading ophthalmic hospitals of the continent recently. Experiments conducted with streptomycin in an eye ointment is far superior to penicillin and sulphonamide therapy.

Streptomycin or dihydrostreptomycin is a stable compound and can be stored at room temperature. It is a bacteriostatic against *M. tuberculosis* and less effective against streptococci, staphylococci, pneumococci and gonococci where penicillin and sulphonamide fail. Its action is more bacteriostatic than bacteriocidal. One per cent streptomycin eye ointment is stable and effective in all infective conditions of the eye.

Application of Streptomycin :—Streptomycin is applied only in an ointment of 1 per cent strength. It is more stable than penicillin and more effective than sulphonamides specially against gram-negative organisms, where an application 3 to 4 times a day is enough.

Indications :—

1. *Acute Conjunctivitis* :—Redness, photophobia and watering, disappear within three days.
2. *Trachoma* :—Streptomycin is less effective than aureomycin.
3. *Infective Conditions* :—Used for styes, ulcers of the cornea or iritis ; streptomycin is equally or more effective than penicillin and sulphonamide.
4. *Infections due to Gram Negative Organisms* :—Streptomycin is definitely more useful than the sulphonamides.

"......Many of the (American) centres have this in common—a change of emphasis in their surgery from technique to chemistry. Consequently one sometimes gets the impression—no doubt erroneously—that some of the young surgeons are chemists practising surgery!"—Harold C. Edwards, King's Coll. Hos. Gaz. summer, 1951, p. 91. (Quoted in Lancet, 2 : 701, 1951).

NINTH BOMBAY MEDICAL CONGRESS

Impressions of a Correspondent

The Ninth Bombay Medical Congress was held in the Breakfast Room of the Taj Mahal Hotel on the 8th and 9th December 1951.

The Conference opened with a welcome speech by Dr. Yodh who gave a brief history of the origin of these meetings. It was inaugurated by Major Gen. S. L. Bhatia, Director General of Health Services and Public Health, Hyderabad. Major Gen. Bhatia who was connected with the Grant Medical College, Bombay, for a period of 19 years, described his coming to Bombay as coming home, and mentioned the Services and Public Health problems in Hyderabad State. He considered that there should be one head for both Public Health and the Civil Medical Administration as opposed to a dual control which exists in a number of major states. From his personal experience, he described how malaria, plague and cholera which were endemic in Hyderabad were mitigated and in some cases completely eradicated.

Dr. S. J. Mehta, President of the Congress, in his speech, deplored the lack of facilities for research in this country and enumerated a number of causes amongst which he mentioned the low standard of payment to a full-time professor, civil servant and research worker. This low standard of pay does not attract the average doctor to that side of the profession, however urgent and necessary it may be. He deprecated the fee-splitting practice amongst doctors which sometimes increases the burden of medical fees on the laity. He also spoke on the educational aspect of the medical student of today and considered that the standard of the students' knowledge had gone down rather than the teaching imparted in the hospitals.

The Presidential address was a departure from the previous Congresses where the function of a President was to thank the various organisers and to throw a tea-party on the social side of the Congress. Dr. S. J. Mehta has done a very wise thing in departing from the usual practice and giving a presidential oration which should rightly aim at criticising constructively the problems of medical politics, education and research in Bombay. It is not too much to hope that the future Presidents of the Bombay Congress will continue this practice.

Dr. Mehta gave a reception at the Roof Garden of the Ambassador Hotel in the evening of Sunday, the 9th December, which was attended by more than 150 people and which served the very useful purpose of social contacts, not only amongst the speakers but also among practitioners and friends.

Among the papers read at the Conference was 'Hospital Administration' by Dr. P. M. Sangani, Supdt. of Sir H. N. Hospital, who rightly stressed the necessity of specialisation in hospital administration. It is not easy for a professor to run a hospital just because he has a postgraduate medical qualification. Association of hospitals and its administrators will bring about some further co-operation in the problems of administraton which are common all over the country.

Dr. Miss S. C. Buch gave a summary of the work done by her on Rh factor, and Dr. K. V. Kulkarni of Haffkine Institute mentioned the occurrence of Rh sensitization in Bombay. Dr. G. D. Adhia mentioned the use of replacement transfusion in such Rh factor cases and other conditions.

Paper on intravenous iron therapy was read by Dr. N. S. Variava who considered that iron by injection was a very good method of treating commonly prevalent iron deficiency anemias of our country.

Some experiments in the use of oral vitamin B_{12} were mentioned by Dr. J. C. Patel. He considered that in the majority of cases of tropical macrocytic anemia 100 μg. of vitamin B_{12} sometimes even 50 μg. per day would be quite adequate to produce hemopoietic response.

In a symposium on peptic ulcer, six speakers took part. They considered the different aspects of peptic ulcer.

The Congress was very well attended and, even though it started as a wartime measure to bring the civilian and armed forces together, it has gained strength and we hope that next year we will have a better standard of papers.

ST. THOMAS' HOSPITAL GAZETTE, Medical World, 74 : 584, 1951.
Examination Failures.

Medical teaching starts early and the study of the English language suffers accordingly. The writer is convinced that many failures are due more to incoherence than to ignorance.

CLINICAL MEDICINE, Medical World, 74 : 541, 1951.
Statistically Speaking

The human heart beats, on the average, 70 times a minute, 100,800 times a day and 2,575,440,000 times in a life span of 70 years. The blood vessels have a combined length of about 100,000 miles, the capillaries have, together, a surface area of one acre. The heart pumps with each beat five ounces of blood into the circulation, which amounts to 22 pints a minute, 1,500 pints an hour, and 4,000 gallons a day. The heart generates sufficient energy within 2 hours, to lift a weight of 65 tons one foot in the air.

Each kidney has about 1,200,000 nephrons, each about 2 inches long, so that the combined length of all nephrons in an adult would amount to 75 miles. The length of individual capillaries in a glomerulus is about one inch; thus, the total of all capillaries in both kidneys would measure more than 37 miles. The entire filtering surface of all glomeruli exceeds twice the body surface.

In an adult there are approximately 300,000,000 alveoli in both lungs with an aggregate surface of 700 square feet. The adult absorbs more than 20 cubic feet of oxygen in 24 hours, and the blood releases more than 20 cubic feet of carbon dioxide within the same period.

LETTER TO SUBSCRIBERS

DEAR READER

With the commencement of this year the Indian Journal of Medical Sciences enters the 6th year of its existence having completed a period of 5 years successfully. During this period, we have tried to keep up, a high standard and have provided you with material of clinical interest therapeutic notes, medical progress reviews and a review of current medical literature. During the last year, our total number of pages was 794.

From the January issue we introduced a new feature called the "Practitioner's Section" which aims at giving material of practical value to practitioners and even consultants. It also includes light reading in the form of "Tit-Bibts." We shall also be prepared to answer any queries sent in by our readers, and with their permission, some of the answers will be published in the Journal.

Printing and paper costs have gone up tremendously during the last year. The subscription of Rs. 10 which we have kept ever since the inception of the Journal does not come up anywhere near the cost of the printing and it is entirely due to the honorary services of the Board of Editors and the co-operation of a number of the Authorities who have been consulted from time to time, that printing and editing at a high standard has been possible. We may not have been able to cater to all our subscribers' needs because of our primary aim, which is to print reading material of a high standard which will enhance the prestige of the medical profession in India, not only in this country but also abroad. Any suggestions from our readers, with a view to improving the Journal, will be welcome and will be considered by the Editorial Board. Hoping to receive your co-operation in the future as in the past.

Board of Indian Journal of Medical Sciences.

I don't really want to know in physiological terms why I like marmalade and coffee for breakfast and jam and tea for tea. Nor do I want to measure the effect that taking sugar in my tea has on my sense of smell and appetite. But some Americans do. Although they're so home they want to have science right at the table with them, and it's got to be real scientific-sounding science. They've found that you can taste sugar in water when it isn't strong enough to interfere with smell and appetite, but they don't put it that way. Here's the conclusion to this important study :

"Experiments are described which demonstrate that in normal individuals the lowest concentration in which sucrose can be detected by means of gustation, differs from the lowest concentration in which sucrose (in the amount employed) has to be ingested in order to produce a demonstrable decrease in olfactory acuity and a noteworthy conversion of sensations interpreted as a desire for food into sensations interpreted as a satiety associated with ingestion of food."

I must try this on my small son who likes science. I shan't ask if he's had enough next tea-time ; I'll ask him if his sensations interpreted as a desire for food have been converted......If I can learn it all by heart in time.

In England Now, Lancet, 2 : 735, 1951.

BOOK REVIEW

Review of Physiological Chemistry By Harold H. Harper, Ph. D., Professor of Biology (Biochemistry), University of San Francisco, Lecturer in Surgery, University of California School of Medicine, San Francisco, Biochemist Consultant to Metabolic Research Facility, U. S. Naval Hospital,Oakland, Director, Biochemist Laboratory, St. Mary's Hospital, San Franisco. Third Edition. Pp. 260, with 13 illustrations. University Medical Publishers, P. O. Box 761. Palo Alto, California, 1951. Price $ 3-50

According to the author the review is intended as a supplement to standard texts in Biochemistry and as a companion volume for students in such courses. The book is also expected to serve the needs for the physicians preparing to state and speciality boards.

Both these expectations of the author have been rightly conceived as is seen from the text of the book. The contents of the book are divided into twenty-one different chapters.

Besides the discussion of the topics in the chapters, the volume includes illustrations, charts and tables at appropriate places with useful information. The main feature of the book is that some figures, charts and tables have been compiled in an unusual and effective manner. The following are some figures that are of special interest: enzyme substrate combination, capillary filtration and reabsorption, plasma proteins, factors affecting net filtration pressure, normal physiology of nephron, abnormal metabolism in uncontrolled diabetes and relationship of pituitary hormone to the target glands and tissues.

The charts that need mention are : tests for the identification of carbohydrates, biological oxidation-enzyme systems, pathways of metabolism of glucose, summary of anerobic muscle glycolysis, Krebs' and Krebs'—Henseleit cycles, fat metabolism and its relation with energy metabolism, and steroid hormones and their derivatives.

The tables showing amino acids essential to the maintenance of nitrogen balance, composition of some saline solutions isotonic with blood, relative diagnostic value of various liver function tests in jaundice and liver disease, etc., are quite informative and of unusual type.

This voluminous information, well arranged, makes the volume aptly suited for a student of Medical Biochemistry both at undergraduate and postgraduate level.

R. G. Chitre

In terms of man days India loses about a thousand million days per year on the basis of an estimate of loss of one year per sufferer from tuberculosis.

Chairman's Report, Tuberculosis
Association of India, 1951.

CURRENT MEDICAL LITERATURE

MEDICINE

EXPERIMENTAL AND HUMAN ATHEROSCLEROSIS : POSSIBLE RELATIONSHIP AND PRESENT STATUS, Braugor, M. and Oppenhem, E. : Bull. of the New York Acad. of Med. 27 : 539-559, 1951. 106 references.

Arteriosclerosis, in which there is deposition of lipids in the intima, is discussed by these authors. It has been well known that the disease occurs as the age advances but it is not the exclusive stigma of age. It has been detected even below the age of 16. It is also known that people suffering from this condition have frequent complications in the form of thrombosis of the coronary and cerebral arteries and this, in the young and in the old, constitutes a major clinical problem. Virchow was the first one to call attention to this condition, and it was soon established that the deposited lipid was mainly of cholesterol esters. The pathogenesis of human arteriosclerosis probably depends on three factors, namely (a) abnormal cholesterol metabolism, (b) constitutional or hereditary disposition and (c) physical and chemical changes in the elastic wall of the artery as influenced by blood pressure, age and ageing, *etc.*,

Table No. 1 gives the reasons how cholesterol plays an important part in the aetilogy of the condition.

TABLE 1.—*Reasons for Implicating Cholesterol as an Important Etiologic Agent in the Pathogenesis of Atherosclerosis.*

1. Cholesterol is constantly present in atherosclerotic plaques.
2. The oral or parenteral administration of cholesterol to susceptible animal will result in the production of atherosclerotic lesions in the elastic arteries.
3. With the exception of macromolecular substances, *e.g.*, polyvinyl alcohol methyl cellulose, pectin and acacia, no agent other than cholesterol will produce the typical atherosclerotic lesion.
4. Intimal lipid deposition and atherosclerosis are rare in wild animals, which seldom, if ever, eat a meal containing the amount of fat found in the average human diet.
5. Human atherosclerosis is prominent in those clinical states accompanied by hypercholesterolemia, *e.g.*, diabetes mellitus, myxedema, nephrosis, familial hyperlipemia, primary xanthomatosis, etc.
6. Atherosclerosis is rare in peoples consuming low or nearly fat-free diets.
7. Atherosclerosis decreased notably in war-torn areas during the fat-shortage years immediately following World War I.
8. Atherosclerosis is more common in obese, overnourished persons than in the lean and undernourished.
9. This lesion is less severe and less common in chronic alcoholics who presumably eat less, especially less fat. for which they have an intolerance.

A large amount of experimental work has been done in the production of experimental arteriosclerosis. Table No. 2 gives the number of animals which are susceptible and which are immune.

TABLE 2. *Experimental Cholesterol Atherosclerosis.*

Susceptible animals	Non-susceptible animals
1. Rabbit.	1. Rat.
2. Guinea pig.	2. Mouse.
3. Dog (with simultaneous thiouracil feeding).	3. Cat.
4. Chick.	4. Goat.
5. Goose (forced feeding).	5. Fox.
6. Golden hamster.	6. Pigeon.
7. Prairie gopher.	7. Parrot.
	8. Monkey.

Table 3 gives the agents which are helpful in the production of experimental cholesterol arteriosclerosis.

TABLE 3. *Experimental Cholesterol Atherosclerosis in the Rabbit.*

Inhibitory agents	Neutral agents	Accentuating agents
Iodides Thyroid Thiocyanate Alcohol Estrogenic hormones in females Androgenic hormones in females	Vitamin A Thiamine chloride Ascorbic acid Vitamin E Desoxycorticosterone acetate Estrogenic hormones in females	Vitamin E (massive doses) Glycocholic acid Cholic acid Olive oil Uranium Thyrotropic factor of anterior pituitary
Alloxan diabetes	Androgenic hormones in males	Lithium iodide } given Pot. cyanide } together
Detergents (intravenous administration of Aerosol OT, Triton NE and Tween 80)	Dehydrocholic acid	Detergents (oral administration of Triton NE and Tween 80)
Lipotropic agents (?) Choline Lipocaic Soya lecithin Betaine Methionine Inositol Benzol	Hyodesoxycholic acid Desoxycholic acid Liver extract Chloroform vapor	

The manner in which the deposition of cholesterol occurs in the intima is (a) permeability of the intima and (b) the physico-chemical status of cholesterol in the plasma.

Hypercholesterolemia and hyperchylomicronemia might add to the deposition of cholesterol. Obesity and increased intravascular pressure are two other important factors.

The authors conclude : (a) Precipitation of cholesterol in the intima is accelerated by increased concentrations in the plasma of cholesterol, chylomicrons and macromolecular cholesterol aggregates and by hypertension and general obesity ; it is conceivable that some, if not all, of these arteriogenic factors increase the permeability of cholesterol. (b) Some substances like estrogenic hormones enumerated in Table 3 inhibit the precipitation of cholesterol in the intima. (c) The prolonged consumption of foods low in fat and free of cholesterol may inhibit cholesterol deposition in the intima by decreasing the concentration in the plasma of cholesterol, chylomicrons and macromolecular cholesterol aggregates.

J. C. PATEL.

THE TREATMENT OF CLINICAL PNEUMONIA WITH ANTIBIOTICS, Report by a Sub-Committee of the Antibiotics Clinical Trials (Non-Tuberculous) Committee of the Medical Research Council, B. M. J., **2** : 1361-1365, 7 references, 5 tables.

A trial of aureomycin, chloramphenicol and penicillin was carried out by the Sub-committee of the Antibiotics Clinical Trials Committee of the Medical Research Council, in London, Sheffield and Glasgow. The diagnosis of pneumonia was in the first place a clinical one, and the generally accepted criteria were adopted. Cases diagnosed as pneumonia on admission were allotted at random to one of three treatment groups : (1) aureomycin ; (2) chloramphenicol ; and (3) Standard treatment. The last group was treated with penicillin, a few with sulphonamides. In this series there were 267 cases and the results of treatment in each group were very similar. In this series, 73 per cent of the cases were pneumococcal and many of the rest bacterial. The general conclusion was that for the cases of clinical pneumonia, penicillin was as good as aureomycin or chloramphenicol and sometimes even better. There were slightly fewer deaths in the penicillin group, and in 4 out of 5 of these, the penicillin had been given orally. An analysis of seriously ill patients on admission, and of the deaths, suggested that penicillin was at least as valuable as the other two antibiotics. Drug toxicity was much commoner with aureomycin and chloramphenicol than with penicillin. The treatment with aureomycin was ten times as expensive and with chloramphenicol, nine times as expensive as compared with penicillin.

In this trial, it can be concluded that, in a choice between aureomycin, chloramphenicol and penicillin, it is suggested that penicillin by injection is the best treatment for clinical pneumonia.

ERIC COELHO.

AUREOMYCIN IN THE TREATMENT OF PNEUMONIA. Eadie, M.B., Grist, N.R., and Landsman, J. B. : B.M.J., 2 : 1365-1367, 1951. 2 references, 3 tables.

The authors studied 79 patients suffering from pneumonia, in a comparative trial of aureomycin and penicillin. Both these antibiotics were administered orally. The patients were allocated, in their order of admission, alternatively to the two treatment groups. The first group (40 patients) was given aureomycin; an initial dose of 1 Gm. was followed by 0.5 Gm. every 6 hours for a period of 3 to 5 days. The second group (39 patients) received penicillin orally ; after an initial dose of 80,000–100,000 units, treatment was continued with a dose of 20,000–60,000 units three hourly. The total dose of aureomycin ranged from 7 to 10 Gm. and of penicillin from 1,500,000 to 3,000,000 units. The two groups of cases were comparable in respect of such prognostic factors as age, duration of illness on admission, and bacteremia. The authors concluded that aureomycin is no more effective than penicillin for the average case. In the 4 of the 5 deaths that occurred in patients in whom cardiovascular complications were present, it is suggested that for such patients early treatment, preferably by parenteral routes, is desirable.

ERIC COELHO.

REACTIONS TO INTRATHECAL STREPTOMYCIN, McKay, R. J. Jr., Davies, J. A. V., Berenberg, W., and Lowd., H.M. : J.A.M.A., 147 : 818-821, 1951. 8 references, 1 table.

The authors report untoward reactions following intrathecal medication of streptomycin among 90 patients treated for meningitis. Eight cases have been described in detail. The reactions were serious in 14 cases with 3 probable and two possible fatalities amongst 90 intrathecally treated. The authors observed the following reactions : Shock-like states with slow, irregular respirations; inability to handle adequately the upper respiratory tract secretions; convulsions, cerebellar signs, hyperpyrexia, the temperature rising to its peak 5 to 6 hours after the intrathecal injection. The milder reactions consisted of pallor, irritability, loss of appetite, and stupor. These serious and mild reactions were not identical in each instance and occasionally occurred immediately after the withdrawal of the lumbar puncture needle. The writers further observed that some relationship existed betwen the size of the intrathecal dose and the occurrence of reaction. When equally good results can be obtained without intrathecal medication of streptomycin, discontinuance of such a mode of administration is advocated.

ERIC COELHO.

COMPLETE CLINICAL REMISSION IN THROMBOANGITIS OBLITERANS DURING ABSTINENCE FROM TOBACCO, Gifford, R. W.: Proceedings of the Staff Meetings of the Mayo Clinic. 26 : 241-245, 1951.

A case of thromboangitis obliterans, in which a twelve-year "clinical cure" was obtained following complete withdrawal of tobacco, has been reported and discussed. Whether the beneficial effect of abstinence from tobacco in thromboangitis obliterans accrues primarily from arresting the disease process in the arteries and veins. or whether circulation is improved merely by relaxation of unaffected arteries is hypothetical. That abstinence from tobacco is beneficial and should form the primary basis for all treatment in these cases is not hypothetical but is a well-established fact.

Author's summary
J. C. PATEL.

THE SIGNIFICANCE OF THE OPHTHALMOSCOPE IN RENAL AND DIFFUSE ARTERIAL DISEASE, Keith, N. M. : Proceedings of the Staff meetings of the Mayo Clinic, 26: 222-225, 1951.

Some of the positive contributions made with the aid of the ophthalmoscope to the knowledge of renal and vascular disease during the last thirty years can be summarised as follows :—

1. Albuminuric retinitis is almost always the result of hypertensive vascular disease whether occurring during the course of primary renal disease or as a part of a generalised arteriolar disorder.

2. The acute albuminuric retinitis usually associated with eclampsia in the female has been noted in an adult male.

3. The presence of albuminuric retinitis is of serious prognostic import. Dr. Berkson determined the survival curve in a considerable series of our patients with diffuse arteriolar disease with hypertension, group 4. and found that 90 per cent died in two years after appearance of the retinal changes. However, albuminuric retinitis can recede, as Liebreich noted in 1859. Wagener and I have lately reviewed 15 cases of malignant hypertension in which the evidence seems clear that remission of the

retinopathy occurred, and without definite directed therapy. Whenever, in such cases, retinopathy recedes, whether the recession be spontaneous or owing to therapeutic measures such as sympathetic surgery, specific diets and so forth, the prognosis has improved.

4. The arteriolar changes which are diffusely throughout, the organs of the body may be functional or organic. The latter, so well described by Kernohan, are often sclerotic and occlusive in type and may lead to occlusion of the central artery of the retina or its arteriolar branches. It is worth mention in that in hypertensive diseases we have never observed occlusion of the central arteries of both eyes.

5. The retinal lesions give the examiner a glimpse of the changes and possible dysfunctions that may occur in other organs throughout the body. This is particularly true with regard to the brain.

6. Albuminuric retinitis is accompanied by obvious vascular abnormalities which included increased intra-arterial pressure and arteriolar dysfunction. The exact relationship of these vascular changes to the specific retinal and general pathologic characteristics is not now clearly understood. Further fundamental research is clearly indicated.

Helmholtz, the teacher of physiology, would I am sure, be very happy that his instrument, the ophthalmoscope, will further aid in unraveling this important problem.

Author's summary
J. C. PATEL.

BACTERIAL VARIATION AND CHEMOTHERAPY, Knox, R. : Guys Hospital Gazette, 65 : 241-246, 1951.

Bacteria often breed true—the same characteristics are transmitted in generation after generation with remarkably little variation. Whether or not the chromosome apparatus is of the same nature as in higher creatures, it is quite clear that there is, on the whole, a fairly rigid genetic control.

I think the following points are especially worth noting :—

1. Their remarkable enzymic activity is of great interest, to the chemist.
2. Their small size and importance of the cell surface, to the physical chemist.
3. Their large numbers, to the statistician, and
4. Their rapid turnover and short generation time, to the geneticist. (For example, 20 minutes to a bacterium are as 30-50 years to a human being).

Author's summary
J. C. PATEL.

ANTISERA IN PROPHYLAXIS AND TREATMENT, Parish, H. J.: The Practitioner, 166 : 399, 1951.

Antisera are of three different types : antitoxic, antibacterial and antiviral. The first, being the most effective, is the most used, *e.g.*, diphtheria and tetatnus antitoxins which have not been replaced by modern chemotherapy. The antibacterial type, *e.g.*, anti-pneumococcus and anti-meningococcus sera are now obsolete, and anti-leptospira is much less used than formerly. Antiviral sera, *e.g.*, measles, are used in the limited sense.

They were introduced in 1890 by Behring. Originally, the whole serum was used. Later on, it was modified and purified by fractional precipitation or by enzyme treatment. Serum reactions became less with this purification.

ANTITOXIC SERA

Diphtheria:—It is still useful, and the intravenous route is used for securing effective concentration of antibody in the blood with a minimum of delay : circulating toxin is neutralized immediately. Penicillin does not replace antitoxin in the treatment of diphtheria. *Streptococcus antitoxin (scarlatina)* :—Most of them are hardly used, but in some parts of England it is still used. *Tetanus antitoxins* : Tetanus antitoxin still remains the most important line of treatment in the disease. It has to be given early intravenously followed by further dosage. The mortality is still high. *Gas-gangrene antitoxins* : Serum for gas-gangrene is hardly used nowadays. *Antivenoms (snake venom antitoxins)* are still the most effective method of treatment for snake bites in this country. Government has provided them free at most of the important centres.

ANTIBACTERIAL SERA

Most antibacterial sera are obsolete, *e.g.*, anti-pneumococcus, anti-meningococcus, anti-leptospira, anti-typhoid, anti-anthrax, anti-plague and anti-erysipeloid.

ANTIVIRAL SERA

The mechanism of antiviral sera is not clear. Viruses do not produce toxins, and hence antisera do not have antitoxic properties. They render viruses inert, probably by uniting with susceptible cells and preventing the specific virus from entering them. The virus in the interior of living cells is protected against antibody action and can therefore multiply. Once the cells have been damaged by a virus, antisera cannot get rid of the consequences. The value of the corresponding serum is therefore prophylactic and not therapeutic.

Antiviral sera are mainly of human origin, derived from convalescent serum. This fact limits its use, and involves a risk of transferring other diseases like homologous serum jaundice. *Measles* :—Convalescent serum protects the child for a period of three weeks. The gamma-globulin has been isolated from crude serum and has been used. *Rubella* :—The gamma-globulin isolated from convalescent serum of the cases has been used by Australian workers in the dosage of 4 cc. for the prevention or abortions, still-births or fetal abnormalities in pregnant women. *Mumps* :—Convalescent serum may prevent orchitis if given within 24 hours of the onset of parotitis. Sera are not used against acute poliomyelitis, influenza, yellow fever, typhus fever, and Rocky Mountain spotted fever. Serum has been suggested for contacts in small pox, but is useless in the treatment. It also has been suggested for rabies.

J. C. PATEL.

PENICILLIN TREATMENT OF ACUTE MASTOIDITIS IN CHILDREN, Black, J. I. M. : B. M. J. 2 : *1191-1193, 1951.*

In this article a survey is made of 118 cases of acute mastoiditis in children treated with penicillin. All the selected cases were true acute conditions. The general condition of the children varied from normal to high fever. All the cases had active otitis media, the duration of otitis media varied from 1 day to 2 months. Majority of the children had little pain, which ceased as the swelling appeared behind the ear. These cases were considered suitable for a clinical trial of penicillin injections because they presented a good clinical picture easy for day to day assessment. They were not, as commonly thought, surgical emergencies, but could quite safely be kept under treatment for a few days. The dosage of penicillin recommended is 300,000 units once daily by intramuscular injection. In 59 cases in which fluctuation was absent resolution to normality occurred without surgical intervention. In the remaining 59 cases, fluctuation was present, and in 38 of them the post-aural abscess was incised In the other 21, absorption occurred naturally. Only 3 cases required mastoidectomy, one of them being a tuberculous infection.

From the experience gained, the author recommends the following routine to treat mastoiditis in children : A careful history is taken to make sure that one is dealing with a new acute infection. An accurate recording of the local and general picture is important as a basis for noting the progress later. The presence of a lymph node enlargement is usually in favour of tuberculosis. Once the penicillin treatment is begun, the patient should be examined daily. Each sign or symptom, local or general, should begin to get better and disappear. A rapid improvement in the general condition and temperature is to be expected. In a few days, the post-aural swelling should show a reduction in size. When fluctuation is present, if the abscess remains the same size for 24 hours it should be incised. If the otorrhoea does not cease in about 7 days, the pus should be examined for penicillin resistant organisms, and appropriate action taken. Should, any new symptoms and signs develop during the course of treatment, all treatment should be continued until the tympanic membrane regains a normal texture and the tympanum is air-containing. There is no prescribed period of treatment which may vary from 3 days to 3 weeks, until the condition is cured. All the cases should be followed up for about 3 months to be sure that hearing returns and that recovery is not retarded by other factors, such as enlarged tonsils and adenoids or sinusitis.

ERIC COELHO.

TREATMENT OF CHRONIC OTORRHOEA WITH CHLORAMPHENICOL, Lewis, R. S. : B. M. J., 2 : 939-943, 1951.

The author presents the treatment of chronic infections of the middle ear and mastoid cavities with a 15 per cent solution of chloramphenicol in propylene glycol. The cases selected here have been all chronic in that the discharge was present for at least 6 weeks. No control was kept.

The method of instilling the 15 pr cent chloramphenicol in propylene glycol was as follows : The patient was kept lying with the affected ear uppermost ; the discharge was mopped as much as possible. Enough of the solution to half fill the external auditory meatus was used. The tragus was pressed in and out a few times to persuade the chloramphenicol solution to enter the middle ear. If the drops are instilled correctly, there will result a bitter taste in the throat. The results obtained by this antibiotic were as good as those produced by any method at present in use. There was less trouble to the patient, hospital or the doctor. The author states that this 15 per cent solution of chloramphenicol in propylene glycol is a saturated one and that it needs no refrigeration. The solution being a saturated one, is self sterilizing. The bottle containing the solution can be kept open, touched with hand or with unsterile wool—but with no evidence of any growth. This work opens a field for further trials and a wider application of chloramphenicol for topical use.

ERIC COELHO.

THE MORNING AFTER THE NIGHT BEFORE, Birch, C. A.: The Practitioner, **167** : 61-64, 1951.

Drowsiness, headache, nausea and foul mouth are the chief symptoms. They are present on waking, and make the sufferer so miserable that he will swear to go 'on the water wagon' in future.

Alcohol is the main factor in its etiology, but not the only one. Others are smoking, bright lights, noise, dehydration from diuresis and the sweating of exercise and dancing. There is also the personal constitutional or psychological factor. Some can drink day after day and feel normal each morning. Others will be ruined by a single late night. The effect is mainly on the nervous system. It is probably due to a depressant action on the higher nervous centre following an early stimulant effect. A single alcoholic bout usually does not cause liver damage but prolonged consumption may cause changes in the liver, but the action is an indirect one by leading to a diminished intake of essential food factors. 'Hang over' is supposed to be more common from mixed drinks than from 'single tract' drinking. It is supposed to be unwise to mix the products of the grain and the grape. However, mixing seems to be unimportant provided the total alcohol content and the volume is the same. Mixed drinks of different flavours often tempt the drinker to drink more. The question of the relation between a 'hang-over' from a concentrated drink and a diluted drink is not settled. However, a maximum blood concentration occurs with a 30 per cent aqueous solution of alcohol. Higher or lower concentrations cause a lower maximum blood concentration. The slower absorption of a higher concentration probably results form damage to the gastric mucosa.

PREVENTION

There are plenty of suggestions, and each drinker has his own scheme. Avoidance of excess is obviously important. Some practicable measures are (1) to drink a large draught of water, lemonade or lime juice before going to bed ; (2) to take water in between the wine ; (3) aspirin before the 'hang-over' begins, or before retiring ; (4) a proprietary combination of aspirin and amphetamine before retiring.

TREATMENT

Self-treatment : (a) effervescent saline, (b) cold douche to the head, (c) aspirin or amphetamine tablets. Treatment of the true alcoholic : If he cannot handle his problem single-handed, he should become a member of 'Alcoholic Anonymous,' where he would make a resolution not to drink any more, for once he has one drink he will not be able to restrain himself.

Treatment when a doctor is called :—Treatment is gastric lavage with sodium bicarbonate which may be also given intravenously. Vitamin B_1 and other members of the B complex may be given to him. Doctors should look for marks of injury and loss of dentures. Erotic adventures are associated with alcoholic bouts. It may be a starting point of schizophrenia. The doctor should keep up his professional secrecy and not be stampeded by officials or by the police. If a doctor is called after some one has been found dead on 'the morning after,' two evanescent pieces of evidence should be obtained : urine or blood should be collected for estimation of alcohol and the rectal temperature should be taken. The last may be useful in finding the time of death. The rate of fall of body temperature after death is approximately 1.5° F per hour, in average room temperatures.

J. C. PATEL.

ECONOMY OF TIME AND LABOUR IN GENERAL PRACTICE, Hartsilver, J. : The Practitioner, *166 : 394, 1951.*

A general practitioner in England suggests how to minimise labour and reduce unnecessary work. A receptionist is indispensable wherever practice approaches 2000 and over, particularly, if one has many elderly and juvenile patients with some private work to do. Much time in writing notes for sending patients to hospitals can be saved by printed forms, an illustration of which is given in the text. Prescription forms with titles of mixtures, linctuses or tablets should be ready. Even if one is making out 40 prescriptions each day, there will be considerable economy in time and labour. *Telephone calls* :—Even though there may be a demand for a doctor to come and talk personally on the telephone, it should be avoided, unless it is a real emergency or someone is dying. Such calls interfere with one's work and peace, and are responsible for much of the unnecessary stress and strain of general practice. The author has found 99 per cent of night calls in his 26 years of practice to be unnecessary. More often, the patient has been ill from three days to three weeks before sending for a doctor. Patients should be trained to avoid such calls, and those who refuse to fall in a line should be recommended to change their doctor—their loss is a welcome relief. Of course, genuine calls are unavoidable. One has to beware of strangers and friends who have other doctors by day. When there is more than one doctor attending the same family, one can easily decline to attend, and in that way you can make them choose one.

In the opinion of this doctor, branch surgeries are a nuisance, and usually wear the practitioner out. He cannot attend two places at the same time. Minor operations in a general dispensary take much longer time and hence should be avoided.

If the patient requires hospital admission, phone calls for finding a room take considerable time and here a receptionist may help.

By making use of these devices, considerable time is saved and there will be more time for other work and relaxation and also for study.

J. C. PATEL.

THE PLANNING COMMISSION, The Antiseptic, 48 : 870, 1951.

The report of this Commission has been before you for a fairly long time and you should by now have become familiar with its contents. While for the advancement of any nation, planning is necessary, I have at the same time to point out that the subjects of public health and medical relief have not received as much attention as they should have been, in spite of the fact that special committees were appointed for the purpose. As pointed out by ex-President Hoover in his appeal to the American people for funds for medical education, "the efficiency of practically all our industry and commerce today is dependent upon the health of their employees and their staffs." Can our planners say that they have kept this basic fact in mind when they prepared their plans? The growth of any industry depends largely on the health of the workers. How can ill-nourished, famished and unhealthy people be able to carry out the plans formulated by the Commission, if no steps are taken to assure them positive health? It is time that the attention of the Government is drawn to this vital defect in their plans so that necessary steps may be decided upon. As the Tamil proverb goes, only if there is a wall can we draw pictures on it. [1] So also, only if we have able-bodied, healthy men and women, can the plans for the development of industries be implemented.

J. C. PATEL.

DERMATOLOGY

TOXIC EFFECTS OF DIAMINODIPHENYL-SULPHONE IN TREATMENT OF LEPROSY, Alladay, E. J. and Barnes, J. : Lancet, 261 : 205 206, 1951.

One hundred and fifty three cases of all types of leprosy were treated by the authors with diaminodiphenyl sulphone (DADPS), the parent sulphone drug, for periods varying from two to eight months. The dosage scheme was 100 mg. daily for two weeks and then 200 mg. daily, administered, orally. The following toxic effects were observed. (1) DADPS syndrome, lepra reaction, neuritis, psychosis, and headache, and hypochromic anemia.

DADPS syndrome is the name given to a group of symptoms developing in the course of DADPS therapy. The onset is usually sudden occurring after 5th or 6th week of treatment. The syndrome consists of dermatitis (papular or exfoliative rash), hepatitis, glandular enlargement and blood mononucleosis (up to 70 per cent) of which dermatitis is the only constant feature in every case. The syndrome subsides after two weeks but sometimes may end fatally. As regards its pathogenesis, the authors feel that it is an allergic reaction rather than a purely toxic one as the syndrome affected more often strong and healthy adults than weaker patients who remained well on the same dosage.

On the basis of the above toxic effects, the authors consider DADPS in a dosage of 200 mg. daily, too toxic for use in leprosy. Next, the drug was further tried in a lower dose *viz.*, 100 mg. daily by mouth for 3 months and then to 200 mg. daily. Even during this lower dosage scheme, another case of exfoliative dermatitis with glandular enlargement occurred with grave illness. From this the authors conclude that though DADPS therapy is cheap, effective and can be given orally, its serious toxic effects even in low dosage, preclude its general use in leprosy.

T. K. MEHTA.

THE CLINICAL RAMIFICATIONS OF INFECTIONS CAUSED BY THE VIRUS OF HERPES SIMPLEX, Slavin, H. B. : Med. Clin. of North America, 35 : 563-569, 1951. 27 references.

In order to understand the vagaries of the herpes simplex infection in man, it is necessary to comprehend what is meant by primary infection by the virus. According to Burnet, if the serum of persons in various age groups is examined for its titre of antibodies against the simplex virus, one may find the titre varying from none to a high amount. Burnet interprets this to mean, that once the human tissues have been invaded by the virus, the latter maintains itself more or less permanently. The virus may be provoked to renewed activity by such stimuli as fever, some drugs, and sometimes without obvious reason. The clinical results of such provocation are usually the classical "fever blister" or "cold sores" on the peri-oral skin or elsewhere on the face. Most of the adult population possess a high titre of antibodies against the virus and this fact is considered as testimony of its frequent latency. What then is the nature of primary infection?

The author feels that it seems well established now, that its most common form occurs during the first few years of life as a stomatitis often accompanied by pharyngitis. This is the commonest form of aphthous stomatitis. In a primary infection, to begin with, there is an absence of antibody in the serum which develops during convalescence, and then persists in 75 to 80 per cent of the adult population. Less commonly the primary lesion may be genital. That genital herpes is principally a venereal disease was stressed by Unna. Little is known about the primary infection in males, but it is well understood in females who get erosions on the labia pudendi. Rather uncommonly the primary infection may take the form of a more or less generalized skin eruption that nearly always appears first in areas of antecedent eczema. This condition was formerly known as Kaposi's varicelliform eruption. At another time it may take the form of dendritic keratitis. An infection of the nervous system is uncommon. In conclusion, the author records the fact that he has seen simplex cases resembling herpes zoster. Zosteriform simplex infection differs from true zoster in that it is often recurrent. There is no mention regarding the treatment of recurrent herpes simplex at different sites,

T. K. MEHTA.

ERYTHRODERMA ICTHYOSIFORME CONGENITUM, Vukas, A. : Arch of Dermat. and Syph., 64 : 36-40, 1951. 3 figures.

Brocq in 1902 was the first to describe the congenital disease characterized by erythroderma and hyperkeratosis of an icthyosis-form covering the whole body. The author came across a fourteen year old boy who presented all the above features. The disease has mainly to be differentiated from another congenital condition called icthyosis vulgaris, which according to some dermatologists is identical with erythroderma congenitum. The author differentiates the two conditions by three criteria, *viz.*, (1) clinical (2) histopathological and (3) by epidermotectoscopy.

Clinically, there is an inverse localization of hyperkeratotic changes in erythroderma icthyosiforme congenitum (E.I.C.)., *i.e.*, it is more marked in the axillae, cubital fossae, popliteal fossae and trunk. The joint surfaces are not involved in icthyosis vulgaris (I. V.). There is no erythroderma in I. V., which is present in E.I.C., and more marked on the face and ears. There is hyperhidrosis of the face, palms, soles and axillae in E.I.C., a feature conspicuous by its absence in I.V. When examined histopathologically, I. V. shows a thickened stratum cornuem, a thinned or completely missing stratum granulosum, a thinned stratum spinosum, well developed papillae and involvement of sudoriferous and sebaceous glands. In E. I. C., the stratum granulosum and stratum malpighi are thickened and in the deeper hypoderm there are a large number of swollen gland orifices. As for the epidermotectoscopy, it is a method for an examination of the skin evolved by the author. It is carried out as follows : "After careful cleansing of the skin with alcohol, any possible rubbing having been avoided, a thin layer from the somewhat tight efflorescence, parallel to the skin surface is cut off with a fine, sharp knife, put on a slide, and examined directly under a microscope with a thirty fold, or if necessary, 50 fold magnification." A local anesthetic (2 per cent novocaine) may be used, depending upon the pain-tolerance of the patient. According to the author, this method permits one to study precisely the surface architectonics of the epidermis, since there are to be detected with it, epidermal pathological alterations in an up-to-now unusual perspective. Six photographic figures, three each of E. I. C. and I. V. are presented with the test. Although certain differences can be noticed in the epidermal pathological configuration by comparison of epidermotectograms of these diseases, no conclusions can be drawn on the basis of a single case. The method has been recommended by the author for a further trial in a larger series of cases for detailed analysis of superficial morphologic pictures. There is no mention of the treatment of the condition.

T. K. MEHTA.

NUTRITION

ON THE RELATION OF DIETS TO THE DEVELOPMENT, PREVENTION AND TREATMENT OF CANCER, WITH SPECIAL REFERENCE TO CANCER OF THE STOMACH AND LIVER, Sugiura, K.: New York, J. of Nutrition, 44 : 345, 1951.

Results of investigation on the effect of individual components of the diet on the development of liver cancer with carcinogenic agents are described.

Young adult rats put on a rice diet containing butter yellow developed cancer of the liver in the course of 3 to 5 months, 75 per cent of these being cholangioma in type. If the diet was supplemented with carrots or 18 per cent casein, the animals were found to live longer ; however the prolongation of life indirectly helped in the formation of larger cancer nodules, mostly of the hepatoma type. The author suggests that the state of nutrition probably influences the type of tumor which develops.

The study was extended to determine what other dietary factors influence the experimental production of cancer. It was found that addition of 15 per cent yeast or 10 per cent beef liver to butter yellow-rice diet inhibited the onset of the malignant process. However, reduction of the quantity of these two factors in the diet, proportionately increased the incidence of malignant changes in the liver. It is claimed that yeast and dried liver (beef) contain probably a substance which protects the rats from development of liver cancer when fed butter yellow. This protective effect was a temporary one, since, in a majority of the animals, it only postponed the onset of malignant changes. Only a small percentage of the animals was completely protected throughout life.

It was found that cancerous changes were observed as early as 60th day, if relatively large quantities of butter yellow were fed with the basal rice diet, while rats fed on butter yellow for shorter periods, failed to show liver changes, if the feeding of the carcinogen was discontinued. However, once hyperplasia has taken place, and early cancerous changes established, it is very difficult to reverse the process, even by the administration of yeast, whole milk powder or liver.

The problem was pursued to determine what exactly was the substance in the yeast and liver which afforded this protection. Administration of riboflavin to the extent of 200 mg. and 2 Gm. of casein per day appeared to have a protective effect though not complete. Supplementation with biotin, unlike the other members of the B complex group, failed to protect the animal against induced cancer. On the contrary, biotin was found to "break down" the protection. This was confirmed by the observation of the existence of an anti-carcinogenic effects of egg white or avidin when fed to the animals.

K. S. RAMANATHAN.

THE ROLE OF VITAMIN E IN THE PRODUCTION OF NUTRITIONAL LIVER INJURY IN RATS, Goettsch, M. : J. of Nutrition, 44 : 443, 1951.

A detailed investigation on liver injury in albino rats deprived of vitamin E on a low casein diet is described. Under these conditions 95 per cent of rats died suddenly in a few weeks time as a result of acute massive necrosis, confirmed histologically. A few of the above animals also showed histological evidence of muscular dystrophy. The animals which survived, failed to grow and manifested typical symptoms of vitamin E deficiency in the form of muscular dystrophy, sterility, *etc.*, though lesions in the liver were absent. The incidence of massive hepatic necrosis was not influenced by the alteration of the lard content of the isocaloric diet nor was it influenced by supplementation with choline or inositol or both. The study was extended to find other factors which influence the incidence of massive hepatic necrosis in rats on low vitamin E and low casein diets. It was found that the incidence of necrosis depended on the amount of tocopherol supplied during the pre-experimental period. Rats receiving tocopherol did not develop massive hepatic necrosis, but they developed fatty infiltration of the liver leading to diffuse hepatic fibrosis. The initial body weight was also found to be capable of influencing the incidence of necrosis, since animals with a low body weight were found to develop hepatic necrosis in greater numbers than larger animals. Increasing the protein content of the diet or including the sulphur containing amino acids, such as methionine or cystine, were found to decrease the incidence of massive hepatic necrosis but every one of the animals suffered from the well known symptoms of vitamin E deficiency. Increase of protein in the form of yeast failed to protect the liver. Addition of very small amounts of methionine failed to prevent the onset of fatty infiltration and hepatic fibrosis, while cystine, if added, aggravates the intensity of the lesion. It is suggested that higher concentrations of methionine would have prevented the diffuse hepatic fibrosis. The literature on nutrition and liver injury is briefly reviewed.

K. S. RAMANATHAN.

VENEREAL

Syphilitic Optic Neuritis, Graneson, G. S. : J. Neural, Neurosurg. and Psychiat. **13** : 216-220, 1950.

Syphilis of the nervous system is divided into parenchymatous and meningovascular syphilis. The author feels that the application of this classification to syphilitic disease of the optic nerve has been neglected. According to the author, besides primary optic atrophy, there is an ill-defined entity of inflammatory neuritis of the optic nerve. The author has described three forms of optic neuritis : (1) as an exacerbation of congenital syphilis ; (2) in association with secondary syphilis, and (3) as a part of late meningo-vascular syphilis.

Clinically, the onset is sudden with a blurring of vision which may deteriorate further or improve spontaneously. Although a headache or an ocular pain is a frequent complaint in the common acute retrobulbar neuritis, it is surprisingly rare in syphilitic optic neuritis. The author came across five such cases of syphilitic optic neuritis. One was associated with secondary syphilis and the other four with meningovascular neurosyphilis. The distinctive feature of these cases is the fact that visual defects have been experienced subjectively only in one eye, whereas ophthalmoscopic changes have been present in both eyes. This is of paramount diagnostic importance, since other forms of bilateral optic and retrobulbar neuritis produce bilateral visual failure. Fundic changes are typical of papillitis. Serologic tests for syphilis were positive in all five cases.

In contrast with syphilitic primary optic atrophy, the prognosis of syphilitic optic neuritis is good, following adequate antisyphilitic therapy which consisted of penicillin, arsenic and bismuth. Four regained normal vision and the fifth improved considerably.

T. K. Mehta.

There are times when the daily batch of drug firms' leaflets includes some particularly vivid coloured picture of bleeding piles, weeping eczema, varicose ulcers, or the like which puts me off my breakfast; but things might well be worse. Suppose these firms cottoned on to the American idea of singing telegraph boys who can be engaged to warble "Happy birthday to you," and so on, at each milestone of your life. Imagine coming down one morning to find a quartet of aged chemists in the hall, waving buretts and booming out :

"Have you heard the rumourol,
That tromexan and dicoumarol
Are worthy of your notis,
For Coronary thrombosis ?

No, no : give me the piles, eczema, or ulcers every time, After all there's always the wastepaper basket........

—In England Now, Lancet, **2** :784, 1951.

I deduct marks for the consultant who furtively looks at his watch. This is a major gaffe. To look at your watch without being caught is the foundation of all medical practice. Good heavens! Has he never heard of counting the pulse?

I award first class honours to the consultant who never believes a word I say, such as to the one who said to me, an ingenous race, the consultants: "Old fellow, as soon as you told me that boy had knocked his hip and was limping I thought of polio," which is exactly what he should have done. That is what a consultant is paid for.

Do the consultants meet regularly in secret conclave to talk over the best ways of dealing with the G. P. without annoying the brute, and yet without letting the patient die? If so, I should like to listen at the keyhole. It might be humiliating, but it would certainly be instructive. —In England Now, Lancet, 2 : 783, 1951.

FOR PRACTITIONERS

DIABETIC COMA

D. D. Vora.

At one time it was believed that ketosis was responsible for the signs and symptoms of diabetic coma. Ketosis occurs during starvation or after a meal containing fats in very high amount. In the ketosis of diabetes mellitus the physiological trends are similar to those of simple starvation, only much greater in degree. The incidence of diabetic coma has certainly diminished, since the regular treatment of insulin. Now with the team work in a unit, devoted to diabetes mellitus, the mortality due to coma is negligible, if the patient is brought under the care very early in the course of the coma.

Mechanism of ketosis :—Formerly, it was believed that fats burnt under the fire of carbohydrates. When the fuel (carbohydrate) was not sufficient, the oxidation did not proceed to completion and the soot (ketone and other ketone bodies) was the result. Now that conception is given up. Ketones are the normal products of fat metabolism, and are produced at one stage. They serve as fuel to the tissues, but are given a second preference to glucose which is burnt easily by them. In the absence of sugar the ketones are utilized by the tissues as the source of energy. The present view, is that, in the absence of insulin or when it is insufficient, the blood sugar rises, presumably, from failure to utilize glucose properly at the periphery. This failure encourages breakdown of liver glycogen (glycogenolysis) and then the formation of new glycogen from protein stores (gluconeogenesis). Ketone bodies are produced by the liver in increasing amounts far more than can be possibly used by the tissues in their change-over from carbohydrates to fats. The protein for gluconeogenesis is supplied by the protoplasm of the tissue cells ; and along with the protein go in relatively proportionate fashion the other intracellular constituents, as potassium, phosphorus and sulphur which pass out in the urine in large quantities. Large negative balances of sodium, potassium, *etc.*, thus arise and there is cellular depletion. Due to hyperglycemia, glucosuria and its consequent diuresis set in, depleting the extracellular water which also carries with it considerable amount of sodium and chloride. Accumulation of ketone bodies results in displacement of bicarbonate, which brings about acidosis. Thus dehydration, acidosis, glycosuria and ketonuria, hyperglycemia, and lower blood pressure and collapse which occur as a part of the picture of coma could be explained in view of the above.

The signs and symptoms of diabetic coma are :—

(1) Dry skin and fauces, soft eye-balls, low blood pressure and raised non-protein nitrogen and shock, are due to dehydration.
(2) Glycosuria, ketonuria, are the result of hyperglycemia.
(3) Kussmal's breathing and smell of acetone are the manifestations of acidosis.
(4) Albuminuria with thick, short casts.
(5) Drowsiness culminating into coma.
(6) Severe abdominal pain, resembling acute abdomen.

The last three groups of symptoms are not explained on the above mode of mechanism of ketosis.

Treatment :—The treatment of diabetic coma naturally resolves itself into supplying enough insulin, fluids, and alkalis. Because of the ionic disturbances, the sodium and potassium have to be supplied in judicious amounts, as in the earlier stages there is raised potassium in the tissue fluids. Whereas, with the administration of insulin the gluconeogenesis is diminished or comes to a halt or reversed and simul-

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ORIGINAL ARTICLE

LIVER FUNCTION STUDIES IN MALARIA *—I

P. N. Wahi‡ and M. M. Arora‡

Few attempts have been made to assess the functional derangement of the liver during the course of naturally acquired malaria. In this country where malarial affections are very common, the main problem related to the recognition of chronic hepatitis is the question of the contribution of malaria to the enlargement of the liver. During our recent studies on epidemic hepatitis, we felt a great deal of difficulty in trying to decide whether some of the manifestations of liver functional derangement were related to chronic malaria. Quite a large number of cases of epidemic hepatitis gave a history of repeated attacks of malaria and the assessment of the liver function test results in these cases was a matter of speculation rather than of facts. Similar difficulty has been encountered in cases of cirrhosis of the liver. The discovery of certain types of functional impairment in a patient with an enlarged liver would ordinarily suggest the possibility of cirrhosis, but if the patient had previously suffered from attacks of malaria, then chronic malaria involving the liver might well explain the findings.

A search of the literature fails to reveal much concrete evidence as to the degree and nature of the liver derangemet in acquired malaria. Most of the text books of tropical medicine discuss this phase of malaria from a clinical point of view only. Recently, several publications bearing on this problem have appeared. Most of these studies, however, have been conducted on neurosyphilitics treated with therapeutic malaria. Although this has enlightened us on the so called acute malarial hepatitis, it has not helped with the understanding of the nature and degree of involvement of the liver in chronic malaria.

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* Paper read at the Annual Conference of the Association of Pathologists of India, at Hyderabad, in November 1951.

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The above considerations led us to undertake a critical study to determine the degree of liver involvement in acute and chronic malaria.

REVIEW OF LITERATURE

Probably, the first to investigate hepatic derangement in malaria under controlled conditions, were Sinton and Hughes[40], who performed a levulose tolerance test in 15 cases of acute falciparum malaria, which were not showing pernicious symptoms. Some of these cases revealed an abnormal curve. This was considered to be due to definite interference with the glycogenic function of the liver. No correlation between the degree of rise in the curve and the severity of the lesion was obtained.

In uncomplicated naturally acquired malaria, Kingsbury[12] and Sehachsuwarly[37] obtained serum bilirubin levels within normal limits. So[42] noted a relationship between the excertion of urinary urobilin and the excretion of the dye azorubin-S in acute naturally acquired malaria. The reduced excretion of the dye associated with the increased urinary urobilin was considered an indication of hepatic damage. He found the most pronounced changes during the fever, particularly in malignant tertian infection. He further observed that the Takata-Ara and dye excretion tests were independent of each other and could not be correlated. Slatineau and Sibi[41], and Phocas[31] have noted transitory hepatic insufficiency in nearly all their cases of naturally acquired malaria.

Mirsky *et al.*[26] reported on a detailed study of 10 patients infected with *Plasmodium vivax* and *Plasmodium falciparum*. The cephalin cholesterol flocculation test was noted to be positive in all cases at some time or the other during the disease. These workers also voted that when the clinical condition improved, the cephalin cholesterol flocculation value returned to normal. They further observed that the patients treated with a high carbohydrate, high protein and high vitamin diet, showed a rapid disappearance of the positive cephalin cholesterol flocculation, while the patients not treated in this manner, revealed a positive cephalin cholesterol flocculation test for as long as a year after the last attack.

Kern and Norris[10] obtained increased total serum bilirubin in some cases and bromsulphalein retention in others, both indicating deranged hepatic functions. McCorkle[25] studied the liver functions in 55 cases of a severe type of malaria by means of the hippuric acid synthesis test. It was observed that 8 patients had deranged hippuric acid synthesis. All these cases had an icterus. He further noted that the test was negative on about the twelfth day of quinine therapy.

Carter and Maclagan[2] have recently investigated 35 cases of *Plasmodium vivax* infection in the acute stage from the point of view of liver damage. They noted that the colloidal gold flocculation was positive in 33 cases. Twenty-eight cases showed thymol turbidity values above normal. In 7 cases, in whom the tests were repeated during therapy, it was noted that the liver function values returned to normal after 3 weeks of treatment.

Makari[19] has reported on the behaviour of the cephalin cholesterol flocculation reaction in malaria. He observed a positive flocculation reaction in 91.4 per cent of cases of acute malaria. He found that the test tended to be negative with antimalarial treatment. Schneider and Shallenberger[38] observed that approximately one third of all acute acquired malaria cases under atebrine therapy are shown to have a demonstrable hepatic dysfunction as evidenced by the standard liver function tests. The cephalin cholesterol flocculation test was found positive in about two thirds of their cases. According to them the latter test is one of the less specific tests of liver function.

The more critical evaluation of hepatic function tests has been done in patients suffering from therapeutically induced malaria. William[51] found evidence of hepatic dysfunction, in patients given therapeutically induced malaria, using the levulose tolerance test. In most cases the curves became normal soon after the malaria had ceased, but in some of the more serious cases of hepatic dysfunction, the return to normal was much slower. In 4 cases where there were relapses, marked hepatic insufficiency was noted.

O'Leary *et al.*[30] obtained a direct positive Van den Berg reaction in 6 syphilitics out of 400 cases studied during malarial therapy. They were of the opinion that the jaundice associated with inoculation malaria was not entirely due to blood destruction, and that there was a hepatic factor involved. Similar views have been expressed by Wile and Sams[50], and Kopp and Soloman[14]. O'Leary *et al.*[30] observed bromsulphalein retention in 6 cases out of 400 studied by them. Six per cent of the syphilitics treated with malarial therapy were noted by them to develop jaundice.

Kopp[13] noted that malaria infection interferes with the synthesis of albumin. He observed a marked lowering of the plasma albumin with varying changes in fibrinogen and globulin at the onset of the paroxysm in induced malaria. Kopp and Soloman[14] investigated liver functions in therapeutically induced benign tertian malaria in 9 neurosyphilitics. Before the start of malaria therapy, 8 out of these 9 patients were found to give normal values for all tests except a slight retention of bromsulphalein above normal in 4 of them. During malaria therapy all these cases showed deranged hepatic function as judged by bromsulphalein retention, reduced hippuric acid synthesis, positive cephalin cholesterol flocculation, reduced fibrinogen concentration and a fall in the total blood cholesterol.

Fredricks and Hoffbauer[7] studied liver functions in induced malaria. They observed increased total serum bilirubin in 24 out of 29 cases ; cephalin cholesterol flocculation was positive in 24 out of 28 cases, urobilinogen was significantly raised in 9 out of 13 cases and 5 out of 8 cases showed bromsulphalein retention, in 3 of whom the dye retention decreased in the course of therapy. They summarised their findings by stating that all the cases studied adequately showed some evidence of hepatic dysfunction.

Glen *et al.*[8] have reported on their observations on liver function studies in therapeutically induced malaria. According to them "The liver is involved in every case of malaria, showing some degree of dysfunction by various tests." The function of detoxification, as studied by hippuric acid synthesis, was depressed for the longest period. It was suggested by these workers that atebrin and mapharsan, given to their patients during the studies, might have contributed to the prolonged depression of this function. They further observed that the liver involvement in malaria is not of the severe type since all the other functions returned to normal in a short period. The cephalin cholesterol flocculation test was noted to return to normal more slowly than the other tests.

Macgraith[16] has recently stated that "malaria infection can bring about an inhibition of certain liver functions, even in the absence of the usual signs of hepatic insufficiency. Such disturbances are of a transitory character and except in cases where the liver is grossly damaged, restoration of normal liver functions takes place rapidly after the malaria attack. After a single attack little in the way of permanent damage occurs".

Studies on hepatic functions have been fewer in chronic malaria as compared to the acute type. Rudolf[36] and Kern and Norris[10] have observed signs of hepatic damage in all forms of human malaria and at all stages of the disease, whether in the primary attack or in subsequent relapses.

Lippincott *et al.*[15] carried out liver function studies in cases of chronic relapsing *Plasmodium vivax* malaria. They noted that a transient derangement of hepatic functions occurred in some cases but there was no evidence of permanent hepatic damage. They noted that with the bromsulphalein retention test, 4 per cent of the cases had abnormal values on the second or third day of the relapse, one per cent had abnormal values on the sixth or the seventh day and 3 per cent had abnormal values after the attacks. A total value of 2.4 per cent abnormal bromsulphalein retention was found in their cases of chronic relapsing malaria. With the cephalin cholesterol flocculation test they had 82 per cent positive results during the first five days of the relapse of the disease. Following the attacks, 20 per cent of the cases had positive cephalin cholesterol flocculation test. The albumin-globulin ratio was not significantly disturbed in their series of cases. In 20 per cent of cases the values of total serum bilirubin were greater than 0.5 mg. per cent upto the fifth day of the relapse of fever. From the fifth day onward, the serum bilirubin levels were found within normal limits. In 3 per cent of cases the galactose tolerance test was abnormal. The hippuric acid synthesis test was abnormal in 23 per cent of cases.

PURPOSE OF THIS STUDY

From the above review of the literature it is evident that liver function studies in acquired malaria and especially in chronic malaria are few. Even those which have been done include a study of one or two particular tests. It was therefore thought desirable to employ a larger number of tests in each case and to chart the results in composite liver function study charts. The latter procedure was adopted in order to study the possibility of obtaining a set pattern of the chart, especially, in chronic malaria, so that it may be possible to differentiate the enlargement of the liver by malaria, from that of a cirrhotic liver, by liver function studies only.

MATERIAL AND METHODS

The material presented consists of liver function studies on 110 cases of malaria ; of these, 50 were acute and 60 of chronic malaria. These cases were derived from the In-patient and Out-patient departments of the Sarojini Naidu Hospital, Agra.

The data presented, and the procedures adopted, are those of the Liver Research Laboratory of the S. N. Medical College, Agra.

Serum bilirubin was determined in the Leitz Photoelectric colorimeter by the method of Malloy and Evelyn[21]. Values greater than 0.6 mg. per cent, for the total serum bilirubin read at 30 minutes, were regarded as abnormal. The maximum value taken as normal for the total serum bilirubin was considered to be 1 mg. per cent. However, the highest value in our laboratory in normal cases was 0.4 mg.

Total plasma proteins, albumin, globulin and fibrinogen were measured according to the King's nesslerisation technic. Normal values for total proteins, as determined in our laboratory, lie between 5.34 and 7.81 Gm. with an average of 5.98 Gm. per 100 cc. of plasma; for albumin, from 3.47 to 4.96 Gm. per cent with an average of 3.96 Gm per 100 cc. of plasma; for globulin, between 1.46 to 2.74 Gm. with an average of 2.21 Gm. per 100 cc. of plasma; and for fibrinogen, between 0.12 and 0.58 Gm. with an average of 0.28 Gm. per 100 cc. of plasma.

The thymol test was carried out according to the Neefe's[29] modification of the Maclagan's[18] technic. Values of turbidity above 3 units were considred abnormal. This is in variance with Maclagan's[18] finding of an upper normal value of 4 units. Similar findings have been recorded by Maizles[20] and Wahi[46].

The thymol flocculation test devised by Neefe[29] was read 18 hours following the determination of the thymol turbidity and the results expressed as 0 to 4+flocculation. Most of our normal cases showed no flocculation, some showed a suspicious, 1+, 18 hour flocculation; anything greater than 1+ was regarded as significantly abnormal. This is in agreement with the findings of Mateer *et al.*[24] who observed that 95 per cent of their normal sera yielded no flocculation.

Colloidal gold flocculation was performed by Maclagan's[17] technic. Our normal cases showed no flocculation.

The cephalin cholesterol flocculation test was performed according to the directions of Dick[4]. Difco' commercial antigen was used. Readings of 1+ in 48 hours were considered abnormal.

Dick's[4] finding of 1+flocculation in 13 per cent normal sera is in keeping with our finding of 14 per cent. Mateer *et al.*[24] observed that 2, 3, or 4+ flocculation is indicative of some impairment of liver function. Our findings are in agreement with their observations.

Bromsulphalein retention was measured by Rosenthal and White's[35] technic, using the photo-electric colorimeter. Retention of the dye beyond 0.5 per cent in the sample of blood drawn 30 minutes after the injection are considered abnormal.

The prothrombin time was determined by the Iyengar *et al.*[9] modification of Quick's[34] technic. Our figures for the average prothrombin time are 19 seconds. Response to the parenteral injection of vitamin K was also determined and the result charted as a percentage concentration of prothrombin, taking 19 seconds as 100.

Urine urobilinogen was determined by Wallace and Diamond's[48] technic. Values greater than 1 in 20 dilution were considered abnormal.

The results of various liver function tests were charted in a composite liver function study chart prepared with our normal standards.

Besides these special tests, all the cases were hematologically investigated and a routine examination of the urine and feces was carried out.

To rule out kala-azar, the formal test of Napier[28] and sternal puncture examinations were done.

A diagnosis of acute malaria was made by finding the malarial parasite in the peripheral blood.

Chronic malaria was diagnosed on the basis of a positive clinical history and by exclusion of other important causes of liver derangement, specially cirrhosis. Liver biopsies were done in chronic malaria cases, and the specimens so obtained were studied histologically to rule out cirrhosis. This also enabled us to study the structural changes in the liver in chronic malaria.

Liver biopsies were performed in most cases with the Vim-Silverman's needle (Wahi[45]). In some cases the Roholm-Iverson's needle, as described by Volwiler and Jones,[44] was used. The tissue obtained was fixed in formal-saline and processed in an auto-technicon. Paraffin sections were prepared and were stained with hematoxylin and eosin, van Geison's stain for connective tissue, and Foot's reticulum stain.

In many instances the paraffin sections of the biopsies of the liver from cases of chronic malaria were stained by Shrott and Cooper's[30] modification of McNamara's method for protozoal parasites. None of these sections revealed the presence of parasites, though other changes, characteristic of chronic malaria, were seen.

RESULTS

1. Liver Function Studies in Acute Malaria.

Thymol Tests.—The thymol test (turbidity and flocculation) was positive during the course of acute malaria in 13 of the 50 cases studied. The thymol turbidity was positive in 7 cases only (14 %), with figures varying from 4 to 10 units. The following table shows the thymol turbidity in units in 50 cases of acquired malaria in its acute phase.

TABLE 1.—*Thymol Turbidity in Units in 50 Cases of Acute Malaria.*

Turbidity in units.	No. of cases.	Percentage of cases.
1—3	43	86
4—5	6	12
7.5—10	1	2

In 6 cases, thymol turbidity failed to become positive while the flocculation test was definitely positive. Another 6 cases gave strongly suspicious one + readings. Considering that most of our normal cases and 95 per cent of Mateer *et al.*'s[24] cases gave no flocculation, it may be concluded that in 12 cases of flocculation, reading was positive or strongly suspicious while turbidity gave a negative result.

TABLE 2.—*Thymol Flocculation in 50 Cases of Acute Malaria.*

Result.	No. of cases.	Percentage of cases.
0	31	62
+	6	12
+	11	22
++	2	4

The thymol flocculation test appears to be more sensitive in the detection of hepatic disturbance in early hepatitis.

Colloidal Gold Test.—The colloidal gold test was found positive in 13 cases (26%) during the course of the disease, with figures varying from one plus to two plus. The following table shows the colloidal gold flocculation in 50 cases of acute malaria.

TABLE 3.—*Colloidal Gold Flocculation in 50 Cases of Acute Malaria.*

Result.	No. of cases.	Percentage of cases.
0	37	74
+	12	24
++	1	2

In 2 cases, in whom the thymol test (turbidity and flocculation) gave normal values, the colloidal gold flocculation test was positive. In another 6 cases, where the thymol turbidity values were within normal range and the th,mol flocculation gave a strongly suspicious positive result, the colloidal gold test was also negative in all except one case. The thymol test and colloidal gold flocculation test were simultaneously positive in 6 cases (12%). On case in the series studied had abnormal values for the thymol test while the colloidal gold test was within the normal range. In 3 cases both these flocculation tests gave positive results, with the thymol turbidity test giving normal values.

The colloidal gold flocculation test appears to be as sensitive as the thymol flocculation test and definitely superior to thymol turbidity in detecting liver dysfunction in acute malaria.

Cephalin Cholesterol Flocculation Test.—The cehaplin cholesterol flocculation test was strongly suspicious positive in 74 per cent of cases in 48 hours. The following table shows the values obtained in 50 cases of acute acquired malaria after 24 and 48 hours.

TABLE 4.—*Cephalin Cholesterol Flocculation in 50 Cases of Acute Malaria.*

Result.	No. of cases (after 24 hrs.)	Percentage of cases.	No. of cases (after 48 hrs.)	Percentage of cases.
0	29	58	13	26
+	20	40	31	62
++	0	0	5	10
+++	1	2	1	2

Comparing the results of the three flocculation tests, it was seen that the thymol flocculation was positive in 19 cases, colloidal gold flocculation was positive in 13 cases and cephalin cholesterol flocculation was positive in 37 out of the 50 cases studied. There were 4 cases where the cephalin cholesterol flocculation was negative and thymol flocculation and colloidal gold flocculation were both positive. In one case both the cephalin cholesterol flocculation and thymol flocculation were negative while the colloidal gold flocculation was positive. Cephalin cholesterol flocculation, though giving the highest positives, cannot be completely relied upon as a single test indicative of definite hepatic dysfunction. Forty two case; (84%) showed positive flocculation tests in acquired malaria. These figures compare well with the findings of Kopp and Soloman[14], Fredricks and Hoffbauer[7], Carter and Maclagan[2], and Glen *et al.*[8], their results varying from 77.4 to 100 per cent.

Bromsulphalein Retention Test.—It was found to be positive in 64 per cent of cases. In 5 cases, this was the only test positive while the other tests were negative. The following table gives the bromsulphalein retention after 30 minutes of a 5 mg. per kilogram body weight intravenous injection in 50 cases of acute malaria.

TABLE 5.—*Bromsulphalein Retention in* 50 *Cases of Acute Malaria.*

Percentage of dye retention	No. of cases.	Percentage of cases.
0—0.5	18	36
2.5—5	10	20
5.1—7.5	3	6
7.6—10	15	30
10.1—15	4	8

Our figures of positive retention in 64 per cent of cases are much higher than those of 16 per cent positive, as found by Schneider and Shallenberger[38]. This is partly due to their accepting 6 per cent retention as normal. Even if we adopt the same standard, we get 42 per cent positive. Our figures, however, are supported by the finding of 72.8 per cent positive in Fredricks and Hoffbauer's[7] series.

Total Serum Bilirubin Estimation.—It was found raised above 0.6 mg. per 100 cc. in 7 cases (14%) out of the 50 cases of acquired malaria studied in the acute phase. The following table gives the distribution of total serum bilirubin values in the 50 cases of acquired malaria studied in this series.

TABLE 6.—*Total Serum Bilirubin in mg. per* 100 *cc. in* 50 *Cases of Acute Malaria.*

Bilirubin in mg.	No. of cases.	Percentage of cases.
0.0—0.2	15	40
0.2—0.6	28	56
0.7—0.9	4	8
1.0—1.5	3	6

In our series only 14 per cent of cases had a significantly raised total serum bilirubin level. Fredricks and Hoffbauer[7], while conducting liver function studies in therapeutic malaria, obtained a raised serum bilirubin level in 29 per cent of cases. This variation in results is supported by Macgraith[16] who states that in uncomplicated acquired malaria the bilirubin levels have seldom been found to be so frequently raised as in therapeutically induced malaria.

Urine Urobilinogen Estimation.—It was done in all the 50 cases studied in this series and found within normal limits in all except one case in whom it was detected upon 1 in 40 dilution. This case had a raised total serum bilirubin and a positive cephalin cholesterol flocculation test.

Total and Fractional Plasma Proteins.—17 cases (56%) out of 30, in whom these estimations were done, showed some degree of hypoproteinemia as judged from our normal standards of average total plasma proteins of 5.98 Gm. per 100 cc. The following table gives the total and fractional plasma protein values in 30 cases of acute acquired malaria.

TABLE 7.—*Total and Fractional Plasma Proteins in* 30 *Cases of Acute Acquired Malaria.*

	Value in Gm.	No. of cases.	Percentage of cases.
Total Proteins ..	4—5	0	0
	5—5.8	17	56
	5.9—7	13	44
Albumin	1—2	0	0
	2—3	10	33.3
	3.1—3.5	15	50.0
	3.6—4	5	16.7
	1—2.2	17	56
Globulin	2.3—3	13	44

25 cases (83.3%) showed some degree of hypo-albuminemia (our normal average value is 3.6 Gm. per 100 cc.). These figures compare well within the findings of Kopp[13].

Associated with hypo-albuminemia, a slight to significant increase in the plasma globulin level was noted in 13 cases (43%) out of these 30 cases (our normal average value of plasma globulin is 2.2 Gm. per 100 cc.). This finding is supported by the observations of Glen *et al.*[8]

TABLE 8.—*Comparison of Liver Function Tests in 50 Cases of Acute Malaria.*

	Fraction.	Percentage positive.
Thymol turbidity	7/50 *	14
Thymol flocculation	19/50	38
Colloidal gold flocculation	13/50	26
Ceph. Cholesterol flocculation	37/50	74
Bromsulphalein retention	32/50	64
Serum bilirubin	7/50	14

* Numerator represents number of positive tests and the denominator the number of total tests done.

The results have been analysed in table 9 which shows the correlation of positive reactions for each test with the positive reactions given by all the other tests. It is of interest to note that the majority of positive tests were correspondingly matched by other positive tests.

TABLE 9.—*Showing Number and Percentage of Positive Reactions for Each Test as Compared with the Positive Reactions Given by all Other Tests in 50 Cases of Acute Malaria.*

	I	II	III	IV	V	VI	No other positive.
I. Pos. thymol turb. ..	7	7/100	6/85	6/85	5/71	0/0	0/0
II. Pos. thymol floc. ..	7/36	19	10/52	15/79	17/90	4/21	0/0
III. Pos. coll. gold ..	6/46	10/77	13	8/61	7/54	2/15	0/0
IV. Pos. cc. floc.	6/16	15/40	8/21	37	24/64	4/10	13/38
V. Pos. bromsulph. ..	5/15	17/53	7/22	24/75	32	7/22	5/15
VI. Pos. serum bili. ..	0/0	4/57	2/28	4/57	7/100	7	0/0

Numerator indicates number and denominator indicates percentage of positive reaction of test as indicated by the number at the head of the column.

Results of all the tests in this group have been summarised in figure 1 which also indicates their relationship to each other. Ten per cent of the cases had no tests positive, indicating that the liver damage was either absent or so mild as not to produce any functional change. Ninety per cent had one or more tests positive, of which 36 per cent had only one test positive. The nature of this test also varied. It is safer to conclude that none of the liver function tests used was accurate when used alone as an index of hepatic dysfunction.

The results of various liver function tests were charted on a composite liver function chart (chart I). The majority of the cases gave a pattern as shown in the chart. It is clear that the flocculation and bromsulphalein retention tests are the ones which give abnormal readings in the majority of the cases of acute acquired malaria.

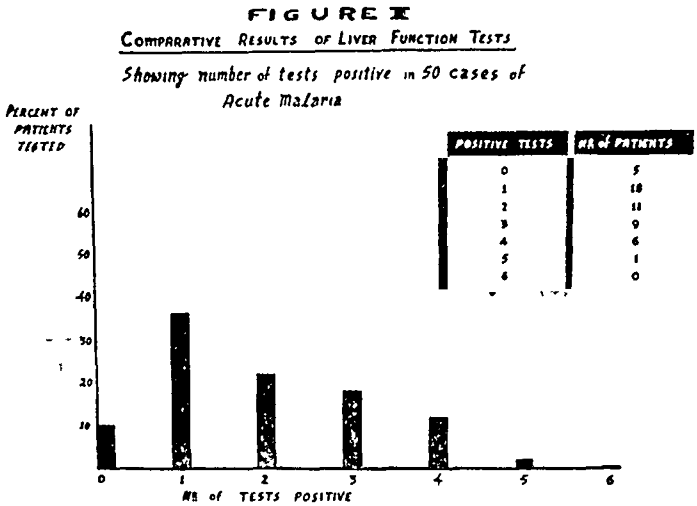

Figure 1.—Showing number of tests positive in 50 cases of acute acquired malaria.

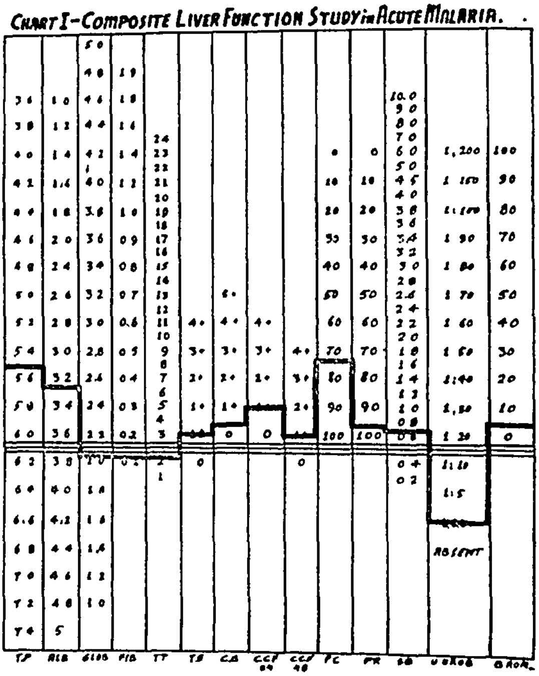

Chart I.—Composite liver function studies-pattern of response in acute acquired malaria.

The relationship between the types of malarial infection and the nature and number of tests showing positive results was also studied. It was found that the type of malarial infection (benign, quartan or malignant) did not determine the nature or extent of the functional derangement. Similar findings, were noted with regard to the number of rigors and duration of acute attacks, which had no influence on the extent of liver derangement.

ORIGINAL ARTICLE

KOILONYCHIA AND PLATYONYCHIA †

P. N. Chhuttani. *

Koilonychia, which means hollow nails, consists of a concavity in the ungual plate. In this paper it is proposed to briefly review the literature and follow it with an account of thirty-five cases of koilonychia and thirteen cases of platyonychia or flat nails. Finally, the nature of the condition will be discussed.

Ball[3] first described the condition but gave no name to it. Crocker[9] suggested the term "spoon nails" in 1896, and Heller[13] introduced the word "Koilonychia". He described how nails became gradually thinner and more brittle, their convex surface was transformed into a concave one, and the edges became raised from the nail bed. The first and fifth finger nails usually escaped. Andreson[2] regarded koilonychia as a component of the Plummer Vinson syndrome. Kaznelson *et al.*[16] stated that koilonychia may occur as symptom of hypochromic achlorhydric anemia. Elovuori[10] reported dull, brittle and concave nails in two women suffering from chronic hypochromic anemia. In one case, the anemia was associated with pregnancy and achylia ; the second case showed an endocrinal disturbance. The nail deformity improved along with the recovery of the anemia. Reviewing the literature he wondered whether the anemia and koilonychia were pathogenetically related, perhaps under the influence of an endocrinal disturbance. In the discussion which followed, Lundholm remarked that out of 51 cases of achylic anemia observed by him, he had noted koilonychia in 39. He had examined 3,500 patients to find koilonychia ; among them he found only one case, a man, who also had typical achylic anemia. Stub observed that he had seen cases of secondary anemia with koilonycia, all in females.

There are several case records in the literature reporting the various combinations of koilonychia with anemia, achylia and dysphagia. Iron therapy brought about an improvement of the anemia and the nail deformity (Cipollaro[6], Broekema[5], Klaber[17], Lewis[18], Weissenback *et al.*[27] Anderson[1], Hernandez,[14] and Clark[7]).

Kartamischew[15] observed koilonychia in three Uzbekistan women and regarded the nail deformity, which was seen in all the nails, to be possibly associated with minor external trauma to the hands, like milking cows and washing food grains. The toe nails were normal. In two cases, platyonychia preceded koilonychia.

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Rosseger[21] reviewed the literature on spoon nails and observed that in the early stages, the disease was more easily perceived by touch than by the eye. The first three fingers of the hand were most often affected and sometimes the toe nails also. He also referred to the reports of koilonychia in coal workers and persons having frequent contact with oils, creosotes, and cresols.

Toegel[24] recorded the case of a 24 year old lorry driver who developed severe koilonychia within the two days after he had done a piece of work using petroleum, turpentine, benzene and benzol. The balls of the fingers became swollen and bluish. He recovered in about 8 weeks. The author was of the opinion that benzol and mechanical pressure deserved consideration as causative factors.

Wyss-chodat[31] reported the case of a boy of 14 years, developed well beyond his age, having no relevant personal or family history, who became affected about a year earlier. All the fingers and toe nails became soft, scaly, thinned, cupped and longitudinally striated. Calcium, phosphorous, vitamins A and D were prescribed and the affection was completely cleared in a few months.

Turpin and Piton[23] reviewed the literature on familial and acquired koilonychia and reported a familial case. The authors thought, that in most cases, koilonychia was a hereditary dystrophy bound up with the 'substitution of an autosomic dominant gene for a normal gene.'

Cooke and Luty[8] described two cases of thyrotoxicosis showing koilonychia and commented that in neither was there any reason for supposing a fault in the iron metabolism.

Pessano and Botbol[20] described the case of a 23 year old mechanic who noticed, 9 months earlier, that the index finger became soft when immersed in water and that the nails became intermittently concave. The condition spread to the other fingers and remissions became shorter, until the deformity of the nails became permanent, three months before he was seen. All the ten fingers had typical spoon nails. Except for a slight lowering of the hemoglobin level, no other abnormality was found. The acid secretion of the stomach was normal. The fingers were exposed to frequent trauma and were constantly in contact with lubricants. To clean his hands he used naptha and cleaning mixtures of saw dust, soda and soap. The author concluded that koilonychia, in this case, was probably due to chemical and mechanical factors. There was no congenital or familial factor.

Pardo-Castello[19] has referred to the occurrence of spoon nails with lichen planus, acanthosis nigricans and prolonged cachexia.

Fox[11] recorded the occurrence of koilonychia with syphilis.

Walzer[26] recorded koilonychia associated with monilethrix and

Wise[30] regarded a case to be due to fungus infection.

White[28] has stated that psoriasis can produce "double spoon-shaped or concave appearance" of nails.

MATERIAL

The thirty-five cases, under report, consisted of two series, the first (19 cases), with the exception of an Arab boy, comprised of Indian soldiers in the Middle East during 1944-45 and the second (16 cases), is a collection at the Medical College Hospital, Amritsar, during 1949-50. Flat nails (13 cases) were studied only with the first series. As the second series is still open, no detailed statistical analysis has been attempted: it is used for a few generalisations or for purposes of illustration.

The army cases came from a relatively static garrison of about 18,188 men: of these 17,000 were meat-eaters and 1,188 were vegetarians.

The nails were carefully examined in 1,863 patients in an army hospital. Fifty-eight cases showed nail changes, 17 showing koilonychia and 41 platyonychia. Five hundred and twenty-seven soldiers doing full duty and in category 'A,' examined for a nutritional survey, showed 2 instances of koilonychia and 15 of platyonychia. All the 19 cases of koilonychia and 3 unselected cases of platyonychia were studied in detail.

Eighteen patients with koilonychia were between 19-44 years, the remaining case being a 15 year old Arab boy. Patients with platyonychia were between 17-40 years of age. The first series consisted of men only. Except one, all were Indians. Six cases came from the United Provinces, one from Madras, one from the North West Frontier Province, one from Iraq and the rest were from the Punjab. The preponderance of the Punjabis was a reflection on the composition of the particular garrison. A similar distribution was seen amongst those with platyonychia.

The daily rations were : 18 oz. (510 Gm.) of atta (wheat flour) or rice, 2½ oz. (70 Gm.) of dal (pulses), 3¼ oz. (92 Gm.) of ghee (clarified butter or vegetable oil), 2/3 oz. (19 Gm.) of condiments, 2 oz. (57 Gm.) of onions, 2 oz. of potatoes, 4 oz. (114 Gm.) of fresh vegetables, 2 oz. of unsweetened tinned milk and 6 oz. (170 Gm.) of fresh mutton with bone for five days in the week. Leafy vegetables were issued for only a few months of the year. In lieu of fresh meat, vegetarians were allowed 4½ oz. (128 Gm.) of tinned milk, three days a week, and ¾ oz. (21 Gm.) of ghee and 3 oz. (85 Gm.) of atta or rice for two days a week, but none of the vegetarians, as a rule, received these. The meat ration of 6 oz. of fresh mutton with bone for five days a week amounted to 4 oz. without bone ; this was checked in local carcasses. The total daily intake was over 3,000 calories and over 80 Gm. of vegetable protein : its iron content was over 20 mg.

Six of the nineteen patients with spoon nails and seven of the thirteen with flat nails were life long vegetarians.

CLINICAL FEATURES

The nail plate often lost its lustre and developed an exaggeration of the fine longitudinal striations. The concavity itself may be marked ; one spooned thumb held eleven drops of water but this was tried in a few cases only. Only occassionally, was the deformity equally developed in all the fingers. As a general rule the first three fingers showed the deformity more often and more marked than the fourth and fifth fingers. This was true, no matter what the etiological factors in the case were. Again, the right hand often showed a greater degree of koilonychia than the left side : none of the patients were left handed. Unaffected fingers often showed flattening of the ungual plate. In those who showed platyonychia only, it was again a general rule to see it more often and more marked in the first three fingers. The right hand in these cases too, seemed to out-do its counter part.

The concavity itself, when not involving the whole plate, was often confined to the central area but in a fair number the anterior one third only, was affected. As the actual casts of the nails were not made during the study of the first series, a more accurate statement cannot be offered on this point. The affected nails were sometimes splintered and the edges often frayed. One patient stated that his nails seldom required paring as the edges kept on getting rubbed off spontaneously. In a

TABLE 1.—*Hematological Values in Flat and Spoon Nails.*

No. of Observations.		R. B. C.		Hb. in Gm.		M. C. H. C.		M. C. V.	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Spooned Nails	19 ..	4.39	1.09	10.85	3.56	26.22	3.41	94.21	17.39
Flat Nails	13 ..	4.57	1.16	12.88	2.88	28.24	1.98	102.00	616.57

Character.	Degree of freedom.	t.	Significance.
R. B. C.	30	0.4477	Not significant.
Hb.	30	1.7073	Not significant.
M. C. H. C. ..	30	1.9214	Not significant.
M. C. V. ..	30	1.3675	Not significant.

TABLE 2.—*Koilonychia—Details of Cases.*

Sr. No.	M/V	R.B.C.	Hb.	MCHC	M.C.V.	Stools.	Kahn.	Free Acid.						Total Acid.					
								R.	1	2	3	4	5	R	1	2	3	4	5
1	V	4.7	15·4	28.2	115.9	H.W.	Neg.	10	6	16	28	40	18	24	22	39	50	66	28
2	V	5·6	14·7	28.09	93.4	No record.	,,	0	0	16	20	8	0	12	24	46	56	30	14
3	M	3·0	6·3	21·0	101.0	H.W. & R.W.	,,	0	0	0	0	0	0	20	16	8	7	14	15
4	M	5·5	14.0	26·2	97·1	Neg.	Not known	56	40	51	10	14	70	68	56	66	26	31	80
5	M	4·6	13·3	28·3	101·8	Not examined	Not recorded	0	0	0	0	20	0	18	16	18	14	36	0
6	M	3·0	4.93	21.5	76·6	H.W.	Neg.	0	10	44	32	16	0	10	22	60	48	38	10
7	M	4·2	9·3	28·4	77.8	,,	,,	0	0	24	0	0	0	12	16	32	0	0	0
8	M	4·7	8·7	20·9	88·2	,,	,,	0	8	30	12	0	0	16	20	41	20	14	0
9	M	4·2	7·95	22.8	82·8	,,	,,	0	0	0	0	0	0	13	18	18	17	20	18
10	M	4.6	8·6	24.9	75.8	R.W. & H.W.	,,	0	4	16	12	16	32	24	40	40	28	46	64
11	M	4.7	11·1	27.5	85.8	H.W.	,,	Not	done										
12	M	5.2	11·62	27.3	81.7	,,	,,	0	16	16	0	16	10	14	44	42	14	36	30
13	M	4.5	8·4	24.08	77.5	,,	,,	0	0	0	0	0	10	10	12	14	12	21	34
14	M	3.6	6.2	2.06	81·7	Neg.	+++	0	0	0	5	0	0	17	14	14	20	16	14
15	V	3·7	14·7	30.6	129.6	,,	Neg.	12	0	12	24	40	24	22	14	24	44	62	40
16	V	1·8	7.0	30.5	127·1	R.W.	,,	0	0	10	16	0	6	20	25	25	28	10	18
17	V	6.6	14·7	27·5	80.9	Neg.	++	0	0	10	16	0	0	10	6	22	32	18	14
18	V	3·95	14·5	30.9	118·6	,,	Neg.	0	17	15	34	32	26	8	32	38	52	42	46
19	M	5.3	14·7	28·6	96·6	,,	,,	62	16	16	36	38	20	76	32	28	54	54	34

NOTE :—M—Meat V—Vegetarian H. W.—Hook Worm. R. W.—Round Worm.

TABLE 3.—*Platyonychia—Details of Cases.*

Sr. No.	M/V	R.B.C.	Mb.	MCHC	M.C.V.	Stool.	Kahn.	Free Acid.						Total Acid.					
								R.	1	2	3	4	5	R.	1	2	3	4	5
1	M	6 40	17.4	29.08	93.6	No record.	Not done.	Not	don	e									
2	V	4·00	9.052	24·46	92·2	H.W.	Neg.	0	15	16	0	0	0	15	29	32	20	12	38
3	M	4·90	9.1	24.5	75·6	Neg.	Not done.	Not	don	e									
4	M	3.70	11·2	27.7	109.0	,,	Neg.	0	0	8	8	18	6	26	22	24	28	38	18
5	V	1·70	7·56	31·5	141·1	,,	,,	12	22	30	40	30	30	22	40	50	64	48	46
6	V	4.00	12.6	28·1	111·7	,,	Not done.	0	6	14	20	40	24	14	18	30	40	54	42
7	V	4·85	15·4	30.06	105.6	H.W.	,,	15	10	40	62	58	30	35	20	50	72	72	40
8	V	3 90	14 0	29.8	125 0	,,	Neg.	8	0	11	26	10	10	21	16	28	36	28	22
9	V	5.76	15·12	28.0	93.7	Neg.	Not done.	16	18	12	20	8	0	30	34	26	32	22	12
10	V	5.30	14.0	28.5	92.5	,,	,,	0	0	14	0	0	0	6	10	28	22	6	10
11	M	4 95	14.0	29 1	96.9	,,	,,	Not	don	e									
12	M	4·90	13.3	28.2	95·9	H.W.	,,	,,	,,										—
13	M	5·04	14.7	28·2	101·1	Neg.	,,	,,	,,										

TABLE 4.—*Gastric Acid Content in Spoon and Flat Nails.*

	No. of Obser-vations.	R *		1†		2		3		4		5	
		Mean.	S.D.	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.
Spooned Nails ..	17	8.24	19.48	6.88	10·64	14.82	14·90	14.41	12·82	14·12	14.77	12.71	18.36
Flat Nails	8	6·38	7.21	8·88	8·77	18·13	11.01	22·00	21.08	20·50	20·67	12.50	13.43
					Gastric Analysis (Total Acid)								
Spooned Nails ..	17	22·47	19·36	24.29	12.90	31·94	16.41	30.71	16·60	32·59	17·23	27·00	21.48
Flat Nails	8.	21.13	9,36	23·63	9.97	33·50	10·46	39·25	19.06	35·00	22·35	28.30	14·53
					Gastric Analysis (Free Acid)								
Nails	25	7·64	16.40	7·52	9·94	15.88	13·63	16.84	15.88	16·16	16.83	12.64	16.65
Peripheral Neuritis	48	6·02	10.25	9.21	9.91	19.25	14.75	22·29	20·22	24.25	21.68	25.69	24.44
					Gastric Analysis (Total Acid)								
Nails	25	22·04	16·60	24.08	11.84	32.44	14.56	33·44	17·50	33.36	18.57	27.48	19.22
Peripheral Neuritis	48	21.31	12·61	24·54	12.89	37·46	17.92	42·27	12.93	41.58	14.60	41·77	27.55

* R=Resting stomach contents. † Half hourly samples for 2½ hours.

few cases of the second series, there were an undepressed verticle central ridge dividing the affected nail into two concave slopes.

The toe nails also showed changes frequently. Of the 19 spoon nails, 5 showed the same deformity in their feet as well, 4 showed no change, and in 10 instances, records were incomplete on this point. Out of the 13 flat nails, 2 showed flattening of the toe nails also. In one case, the toe nails showed well marked spooning when the finger nails were only flattened. Of the 16 civilian cases, 7 showed spooning in the feet, 7 had normal toe nails and in 2, this observation was not recorded.

If anemia was arbitrarily defined as 4 millions or less of red cells per c.mm. and/or 11.6 grammes or less of hemoglobin per 100 cc., then 12 of the 19 spoon nails and 6 of the 13 flat nails were suffering from anemia ; the difference in the incidence of anemia in spoon and flat nails was statistically insignificant. Three each of the spoon and flat nails had a red cell count and hemoglobin level of more than 5 millions per c.mm. and 14.5 grammes per 100 cc. of blood, respectively. Six cases each of koilonychia and platyonychia showed macrocytic anemia (M. C. V.>100 c.μ.) Mean corpuscular hemoglobin concentration was below 30 per cent in all cases except five of the above macrocytic anemias. Thus 'dimorphic' anemia was seen in 7 cases. The average means and the standard deviations of various absolute hematological values in spoon and flat nails are shown in Table 1. The differences between their means were statistically insignificant. For details of individual cases see Table 2 and 3.

Gastric Analysis, after fractional test meal test, was done in 18/19 cases of koilonychia and 8/13 cases of platyonychia (Table 2): two of the former showed achlorhydria. One of these, investigated further, was shown to be histamine fast. A comparison of the average free and total acid content of the various samples in spoon and flat nails showed no significant differences (Table 4). Another similar comparison was made between all these 26 cases showing nail changes and 48 cases of a series of peripheral neuritis. No significant differences were demonstrable.

Ten cases of koilonychia and four of platyonychia showed hookworm infestation.

Two cases of koilonychia had serological evidence of syphilis.

Three cases of koilonychia and two of platyonychia had chronic malaria and splenomegaly.

No one gave a history of blood loss from any source.

In the civilian series of spoon nails, a case each was seen associated with thyrotoxicosis and Addison's disease. Two cases were of the heredo-familial variety.

In the first series, 13 spoon nails were treated with iron ; distinct improvement in the deformity was noted in 11 cases, the other 2 were not observed for more than a couple of weeks. The longest period of observation of the treated cases was 3 months, during which time two cases recovered fully.

None of the flat nails was adequately treated with iron and only 2 cases were observed for more than 3 months. One remained unchanged and in the other flattening became more marked and extensive.

Of the second series, those who had been given iron recovered or are recovering. Spontaneous recovery is not common : a notable example was seen who recovered completely from the deformity, without any treatment. In his case the deformity was not associated with anemia or lack of acid in the stomach ; serological evidence of syphilis was found but he was not given any treatment for it as he was an elusive subject and would not follow advice.

Flattening was suspected to be a precursor of spooning because it was often present in association with the spooned nails. It was not possible to demonstrate any significant differences in the clinical and laboratory findings between cases showing spoon nails and those with flat nails only.

DISCUSSION

What is the nature of the condition? The literature as well as the present material provide adequate evidence that koilonychia may be associated with a variety of unrelated disease states. We have seen it to be present in apparently healthy persons. Can we discover a unitary link in this apparent diversity? This cannot be answered in the affirmative with finality but we can gather clues which point in this direction and lay a hypothesis for further elucidation of the problem. The most common factor is iron deficiency as suggested by the lowered mean corpuscular hemoglobin concentrations and the response to iron. The condition is said to be cured with iron irrespective of the anemia (Waldenstrom[25]). The majority of the reports in the literature show it to be a component of the Plummer-Vinson syndrome, which is an iron deficiency state conditioned by achlorhydria and long demands on the iron stores in women. Indeed, Wilkinson[25] regards koilonychia to be pathognomonic of idiopathic hypochromic microcytic anemia. In our cases there was only one instance of a complete Plummer-Vinson syndrome. Achlorhydria was also uncommon in our cases. This seemingly new state of affairs, is readily understandable when we consider the great frequency of iron deficiency states amongst us and their relationship with malnutrition, protozoal and helminthic diseases.

Serum iron estimations have not been possible in this study, neither have we been able to make a satisfactory study of the iron contents of the affected nails. Glazebrook[12] recorded a case of koilonychia associated with polycythemia vera who had a low serum iron content. Treat-

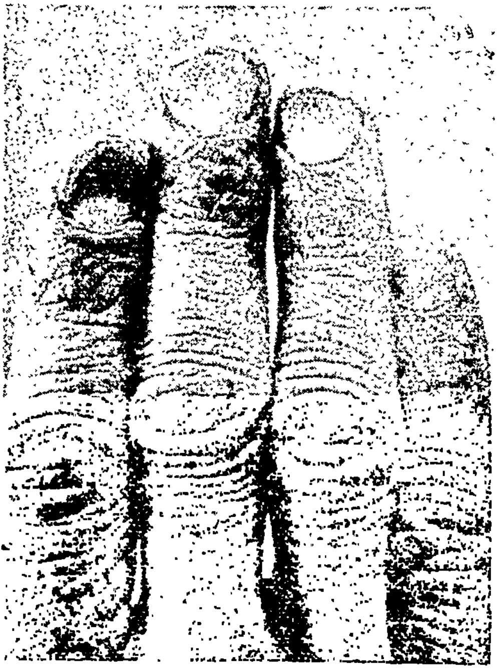

Fig 1.—(*a*) Right hand. Note that the little finger is completely spared but the ring finger is slightly spooned.

ment with roentgen rays reduced the red cell count, increased the serum iron, and the nail deformity healed.

Evidence suggests that koilonychia is generally a sign of iron deficiency whose relationship with idiopathic hypochromic anemia, or anemias in general, is incidental rather than that of cause and effect.

Why is it that only a small percentage of iron deficient subjects develop this nail deformity? The answer is not known. Heredo-familial predisposition has been postulated (*loc. cit.*) but it applies to a very small minority only.

Why and how does the ungual plate go concave? That the nail bed atrophies and the dystrophic ungual plate sinks, is one answer that suggests itself when one looks at the deformity. The terminal phalangeal bone showed no atrophy in the three cases investigated radiologically for elucidating this possibility.

The deformity was quantitatively more marked in the first three fingers: this observation is corroborated by Rosseger[21] (*loc. cit.*) but he did not attempt an explanation. It was also often more marked in the right hand in right handed people (figure 1). That the first three fingers work more than the remaining two and the right hand more than the left, suggests that work was

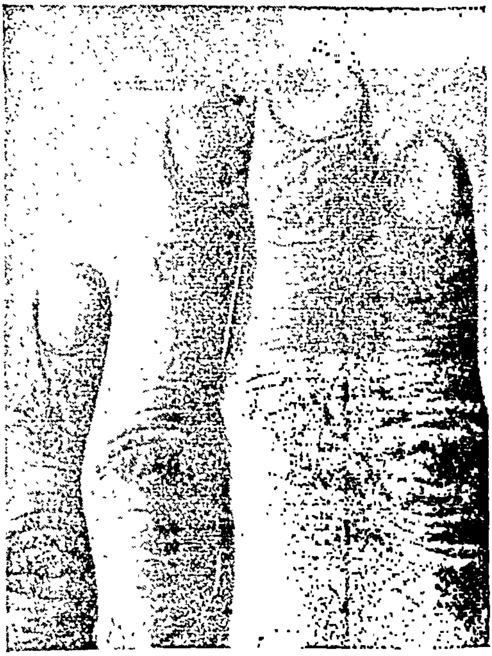

Fig. 1.—(*b*) Left hand. Note that the little and ring fingers are not involved.

quantitatively related with the degree of spooning.

What part does iron take in the nutrition of the nails? Nails are a thickening of the stratum lucidum and consist of keratin, a protein composed of several amino acids such as glycine, leucine, glutamic acid, tyrosine, methionine and cystine. Keratin is stated to be synthesised in the outer parts of stratum germinativum, the energy required for the synthesis being derived from internal respiration (Bradfield[4]) for which iron containing intracellular enzymes such as the peroxidases and cytochromes are important. Iron is also required for the chromatin of the nucleii. Parenchymal iron in the tissue enzymes may amount to as much as 16 per cent of total body iron. Thus, it is not illogical to postulate *that iron deficiency may lead to a poor keratin production*, a defective ungual plate, which not being able to meet the stress and strain of work or mechanical and chemical traumata, may become ridged flattened and subsequently spooned. It is possible to lose as much as 1.32 grammes of iron and still maintain a good normal hemoglobin level : the total body iron content is 4.65 grammes (Sodemann[22]).

Finally, a comparison of spoon nails with clubbed nails is worthwhile. Concavity versus convexity, indifferent lustre versus a shining surface, ridges versus a gloss, hypertrophy versus atrophy, make an interesting contrast. But they have one simulating feature in common : we are equally ignorant about the intricacies of both.

SUMMARY

The literature on koilonychia is reviewed and thirty-five cases of koilonychia and thirteen cases of platyonychia are described.

Platyonychia was regarded to be an earlier stage of koilonychia. Hookworm infestation, syphilis, chronic malaria with splenomegly, thyrotoxicosis and Addison's disease were some of the associated factors present : two cases were of the heredo-familial variety. It was concluded that, as a broad rule, iron deficiency was probably the underlying cause even when there was no overt anemia. The nature of the deformity is discussed.

ACKNOWLEDGMENT

Thanks are due to Dr. R. B. Nanda for making all the nail casts, to Professor Shiv Kumar for constructive suggestions and to Professor Gurubuksh Singh for permission to investigate some of his cases.

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ORIGINAL ARTICLE

ANEMIAS IN DISEASES OF THE GASTROINTESTINAL TRACT *

K. N. Gour † and A. K. Seth. †

In the pathogenesis of anemia, the gastrointestinal tract plays an important role. In fact, after the umbilical cord has been cut, the newly born child has to depend entirely on his own resources for the regeneration of his blood and the whole chain—the gastrointestinal tract, liver and bone marrow—should be in the optimum condition for perfect hemopoesis, apart from an adequate food intake. Any defect in this chain may give rise to insufficient or inefficient red blood cell formation. Of all these, the condition of the gastrointestinal tract demands our closest attention, because as we shall see shortly, even if the food intake is adequate in quality and quantity, the condition of the gastrointestinal tract may upset the balance and may lead to the production of a macrocytic or microcytic anemia.

In the gastrontestinal tract, the stomach, small intestine and large intestine, all play an important part in hemopoesis. Any defect in them is liable to produce different types of blood pictures and consequently different types of anemias. The defects that can arise in this tract may lie in their absorptive capacity, in the production of the various enzymes at different sites, or may be due to parasitic infections of the intestines which may interfere with the assimilation or absorption of hematinic principles or bring about their destruction.

Obstruction, from any cause, at different places may also give rise to defects in the absorption of hemopoetic principles and may materially change the blood of the individual.

Present researches also show that even vitamin B_{12} is formed in the intestines and is excreted in the stools. In cases of pernicious anemia 0.3—1.8 μ. Gm. of vitamin B_{12} are passed in the stools. For this reason there is no doubt that vitamin B_{12} is manufactured in the intestines. There is also a symbiotic action of the organisms in the intestines.

The importance of the gastrointestinal tract in the production of anemia has been studied at the S. N. Medical College, Agra, and records of 960 patients have been utilised for this study. These cases were admitted from January 1941 to December 1950, and out of all these, 400 were associated with gastrointestinal tract disorders. Out of these 400 cases, the different causes which have been responsible for anemia have been shown in Table 2.

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ANKYLOSTOMIASIS

Ankylostomiasis was found in 26 per cent of these 400 cases, and was found at all ages and in both sexes, but more in males than in females. Almost all these cases came from villages and in all of them a history of going to the fields barefooted could be elicited. Their diet was unbalanced and was mostly a poor vegetarian one. They complained of progressive weakness, increasing pallor, breathlessness and palpitation on exertion, diarrhea or constipation, pain in abdomen, anorexia, flatulent dyspepsia, occasional fever, and a few constitutional symptoms like headache and giddiness. On clinical examination, they were anemic, had abdominal tenderness, edema over the feet, a soft systolic hemic murmur in all the areas of the heart depending on the severity of the anemia, and a few had signs of congestive heart failure. Ova of *Ankylostoma duodenale* in the stools were seen in all, and occult blood in the majority of cases. Gastric analysis showed hypochlorhydria or achlorhydria. The blood picture revealed in most cases a hypochromic microcytic anemia while a few had a macrocytic hypochromic anemia.

The pathogenisis of anemia in this disease is a matter of controversy. A chronic blood loss, unbalanced diet, hypochlorhydria, and interference of protein digestion by the presence of worms, as shown by Stewart,[4] are some of the factors which have been attributed to the production of anemia. The theory of a toxic depression of the bone marrow has been disproved by the fact that no evidence of intravascular hemolysis of the red blood cells has been seen and that there is a satisfactory response to iron even if the ankylostomiasis is not treated (Whitby & Britton)[5].

CASE REPORTS

Case 1.—P., a 33 years old male, was admitted with complaints of loose stools, low grade fever and a previous history of having suffered from ankylostomiasis. On examination he was found to be anemic, his tongue was pale and pigmented. Blood examination showed a red cell count of 2.93 million/c.mm., hemoglobin 7.0 Gm. per 100 cc., mean corpuscular volume 82 c.u*., mean corpuscular hemoglobin 24 rr, mean corpuscular hemoglobin content 29 per cent., white blood count 11.500/c.mm., Poly morphonuclears 60 per cent, lymphocytes 25 per cent, eosinophils 8 per cent, mononuclears 7 per cent, and a normal gastric acidity curve. Stool showed ova of *Ankylostoma duodenale.* He was given two courses of anthelmintics and 90 gr. of ferri-et. ammon. citras daily ; after one month, his red blood cell count was 4.1 million/c.mm., hemoglobin 10.5 Gm. per cent, mean corpuscular volume 95 c.u*., mean corpuscular hemoglobin content 28 per cent.

Comments :—The response in this case was seen after oral iron therapy alone, since the gastrointestinal conditions were suitable for the absorption of iron.

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* Please read u as μ

Case 2.—M. D., a 23 years old female, was admitted with a history of weakness, pain in abdomen, breathlessness on exertion, and oligomenorrhea of one year's duration On examination she was found to be extremely anemic, had a pigmented tongue, tender abdomen, and a hemic murmur was heard in all areas of the heart. The stool showed ova of *Ankylostoma duodenale*, gastric analysis showed hypo-acidity, and blood showed a red cell count of 8.0 million/c.mm., hemoglobin 3.0 Gm., per 100 cc., mean cell volume 175 c.u*., mean cell hemoglobin 37 rr., mean cell hemoglobin count 20 per cent and the general blood picture showed anisocytosis, poikilocytosis, macrocytosis, and vacuolation. The white cells were within normal limits. She was given one blood transfusion of 50 cc., 90 gr. of ferri et. ammon. citras daily by mouth and reticulogen 1 cc. intramuscularly every day. After four weeks the red cell count was 2.8 millions/c.mm., hemoglobin 7.0 Gm. per cent., mean cell volume 94 c.u*., mean cell hemoglobin 25 rr., mean cell hemoglobin count 27 per cent.

Comments :—This case showed a macrocytic hypochromic anemia. To start with, this anemia must have been microcytic hypochromic, out because of the long standing history the absorption of the erythrocyte maturing factor must have been rendered defective. This might be due to the mucous membrane of the duodenum and the jejunum rendered unhealthy by a heavy ankylostome infestation.

Case 3.—G. R., a male aged 50 years, was admitted with complaints of pallor, constipation, anorexia and weakness. On examination he was wasted, slightly jaundiced, tenderness in the umbilical region could be elicited. The stool showed occult blood and ova of *Ankylostoma duodenale* : gastric analysis showed hypochlorhydria and the blood showed a red cell count 2.8 millions/c.mm., hemoglobin 7.25 Gm., per cent, mean cell volume 82 c.u*., mean cell hemoglobin 26 rr., and mean cell hemoglobin count 31 per cent. Van den Bergh reaction was indirect positive and the icterus index was 14 units. He was given 2 courses of anthelmintics and 90 gr. of ferri et. ammon. citras daily. Three weeks after, he showed only a poor hematological response, and his blood values were : red cell count. 2·9 millions, hemoglobin 7 Gm. per cent, mean cell volume 76 c.u*., mean cell hemoglobin 24 rr., and mean cell hemoglobin count 31 per cent. He was then given 10 daily intravenous injections of saccharated iron oxide containing 100 mg. of elemntal iron. With this he responded well and his blood, after 4 weeks, showed a red cell count of 4.4. millions/c.mm., hemoglobin 13.5 Gm. per cent, mean cell volume 89 c.u*.. mean cell hemoglobin 30 rr., and mean cell hemoglobin count 33 per cent.

Comments :—The absence of a response to oral iron therapy in this case was due to hypochlorhydria and an unhealthy duodenal and jejunal mucosa which must have hindered the absorption of iron from the intestines.

Case 4.—B. B., a 22 year old male, was admitted with the complaints of diarrhea and weakness for about a year and breathlessness for about 6 months. Clinical examination revealed a tender abdomen, pale tongue ; heart sounds were feeble and a hemic murmur was heard in all areas. Stool examination showed ova of *Ankylostoma duodenale,* gastric analysis revealed hypochlorhydria and blood showed red cell count 2.27 millions/c.mm. Hemoglobin 4.25 Gm. per cent, mean cell volume 84 c.u*., mean cell hemoglobin count 22 per cent. He was given saccharated iron oxide containing 100 mg. of elemental iron, daily, intravenously for 10 days. His blood after 4 weeks showed a red cell count 4.34 millions, hemoglobin 13.5 Gm. per cent, mean cell volume 93 c.u*., mean cell hemoglobin 33 rr., and mean cell hemoglobin count 34 per cent.

Comments :—This case was given intravenous iron from the beginning and showed a response better than that of the oral iron therapy in other cases.

CHRONIC DIARRHEAS

The next most important cause of anemia in this study was chronic diarrhea including chronic dysentery and colitis. This comprised 100 cases out of which 68 (17%) were due to chronic diarrhea, 27 (6.75%) due to dysentery and 5 (1.25%) due to colitis. These patients, besides the symptoms of anemia, complained of blood and mucus in their stool, pain in abdomen, stomatitis and anorexia. On examination they revealed pallor, stomatitis, parrot beaking of the nails and abdominal tenderness. The stool contained blood and mucus ; gastric analysis showed hypochlorhydria. In the pathogenesis of anemia in these conditions, although ulceration, hemorrhage and mal-absorption are the main factors, atrophy of the secretory glands of the stomach has also been observed in a few cases. The macrocytic hyperchromic anemia is due to a lack of absorption of the erythrocyte maturing factor on account of the rapid passage of food through the bowels ; and a microcytic hypochromic anemia is due to chronic blood loss and lack of absorption of iron. Deficiency of vitamins B and C has also been considered a factor in the production of anemia in these cases.

In this series of cases most of the cases of hypochromic anemia responded to oral iron, but in some there was no response due to mal-absorption of iron and in these cases intravenous iron did good. The macrocytic anemia responded to parenteral liver extract therapy or parenteral folic acid therapy. The latter had an added advantage, in that the hematological response was equally good and that it also checked the diarrhea.

Case 5.—T. D., 20 year old female, was admitted for dysentery for 2½ months duration and breathlessness for 1½ month. On examination, she had anasarca, slight ascites, pallor, tenderness of the abdomen, a tender liver, 1" enlarged, feeble heart sounds and a hemic murmur. Stools contained blood and mucus, gastric analysis revealed achlorhydria and the blood values were : red cell count, 1.58 millions/c.mm., hemoglobin 2.5 Gm. per cent, mean cell volume 68 c.u*., mean cell hemoglobin 16 rr, and mean cell hemoglobin count 23 per cent ; the general blood picture showed anisocytosis, microcytosis and vacuolation. She was given bismuth and Tr. belladonna orally and 10 daily intravenous injections of saccharated iron oxide, each equivalent to 100 mg. of elemental iron. After 4 weeks, the red cell count was 3.5 millions/c.mm., hemoglobin, 10.0 Gm. per cent, mean cell volume 94 c.u*., mean cell hemoglobin 29 rr. and mean cell hemoglobin count 30 per cent.

Comments :—In this case the anemia was perhaps due to chronic blood loss and diarrhea. She responded to intravenous iron therapy besides antidiarrheal drugs.

Case 6.—P., a 45 year old female, was admitted for blood and mucus in stools, weakness, and stomatitis. Examination revealed anemia, emaciation, a beefy tongue, tender abdomen and a hemic murmur over the heart. Stools contained mucus blood and pus cells and gastric analysis revealed achlorhydria. The blood showed a red cell count of 2.5 millions/c.mm., hemoglobin 9.0 Gm. per cent, mean cell volume 120 c.u*., mean cell hemoglobin 40 rr., and mean cell hemoglobin count 33 per cent; the general blood picture showed microcytosis, anisocytosis and polychromasia. She was given sulphaguanidine and folic acid 15 mg., intramuscularly on alternate days. She responded well and at the time of discharge, her red cell count was 4 millions/c.mm., hemoglobin 12.5 Gm. per cent, mean cell volume 90 c.u*., mean cell hemoglobin 31 rr., and mean cell hemoglobin count 34 per cent.

Comments :—This case revealed a macrocytic hyperchromic anemia and responded to folic acid therapy. The toxemia, due to infection in colitis, may depress the normal bone marrow activity. If both iron and the erythrocyte maturing factor are lacking, then the result of microcytosis of iron deficiency is counteracted by macrocytosis of the erythrocyte maturing factor deficiency, and the result is normocytic anemia, but by far, the commonest variety is the hypochromic and microcytic anemia.

ABDOMINAL TUBERCULOSIS

Out of 400 cases of anemias of gastrointestinal tract disorders, 13.25 per cent (53 cases) were of abdominal tuberculosis. These cases were usually females of 20-40 years of age and were admitted for one or more of these complaints—abdominal pain, weakness, occasional fever specially in the evenings, anorexia, and constipation alternating with diarrhea. Objective findings were weakness, emaciation, a doughy and tender condition of the abdomen, more marked in the umbilical, epigastric and right iliac regions; glands in the abdomen were often palpable. Blood examination showed a microcytic hypochromic, normocytic normochromic or a macrocytic hyperchromic anemia. Hawksley and Meulengracht[2] in 1936 reported 24 cases of tubercular intestinal stricture having macrocytic anemia. Infection depressing the bone marrow, anorexia, and structural changes leading to defective absorption of principles essential for blood regeneration, are some of the factors responsible for anemia in abdominal tuberculosis.

Case 7.—L., a 25 year old female, was admitted for fever, weakness, pallor, pain and lump in the abdomen, and cough with expectoration for 6 months. She was found to be emaciated, anemic, running fever ; cervical and abdominal glands were palpable, the spleen was slightly enlarged and there was a mass 2" × 2" in the right hypochondrium ; the apex of the right lung showed signs of consolidation. Her stool was normal. Gastric analysis showed achlorhydria and red blood cell count 2.0 millions/c.mm., hemoglobin 7.0 Gm. per cent, mean cell volume 110 c.u*., mean cell hemoglobin 35 rr., and mean cell hemoglobin count 31 per cent. She was given 90 gr. of ferri et ammon citras daily and 2 cc. of liver extract, intramuscularly. on alternate days. After 6 weeks of therapy there was no hematological response. Then she was given streptomycin 1 Gm. daily intramuscularly and after another 4 weeks, her blood values improved to a red cell count of 3.2 millions, hemoglobin 9.5 Gm. per cent, mean cell volume 96 c.u*., mean cell hemoglobin 30 rr., and mean cell hemoglobin count 30 per cent. Besides this, there was also a general improvement in her condition.

Comments :—In this case the anemia did not respond at first to iron and liver extract therapy, because the toxemia persisted and did not allow the utilisation of the hematinics by the bone marrow, but when the toxemia was overcome the response was satisfactory.

TABLE 1.—*The Yearly Incidence of Anemia.*

Year.	Total No. of Anemia Cases.	No. of tract.	Cases of Anemia with G. I. disorder.
1941	53	17	(32.08%)
1942	55	19	(34.54%)
1943	63	24	(32.87%)
1944	77	28	(36.36%)
1945	100	42	(42.0%)
1946	170	54	(33.9%)
1947	103	45	(48.4%)
1948	160	71	(45.2%)
1949	90	29	(32.2%)
1950	89	71	(79.8%)
Total	960	400	(41.6)

TABLE 2.—*The Different Causes of Anemia Associated with Gastrointestinal Disorders. Their Incidence Between* 1941 *and* 1950.

S. No.	Disease.	No. of cases.	Percentage.
1	Ankylostomiasis	104	26
2	Chronic diarrheas	68	17
3	Abdominal tuberculosis	53	13.25
4	Macrocytic anemia (Nutritional)	51	12.75
5	Giardiasis	29	7.25
6	Pernicious anemia	23	5.75
7	Amebiasis	18	4.5
8	Sprue	16	4.0
9	Hypochromic anemia	10	2.5
10	Bacillary dysentery	9	2.25
11	Colitis	5	1.25
12	Cancer stomach	4	1.0
13	Cancer oesophagus	1	0.25
14	Pellagra	3	0.75
15	Hematemesis	3	0.75
16	Pyloric obstruction	2	0.5
17	Plummer Vinson syndrome	2	0·5
18	Intestinal colic	2	0.5
19	Krohn's disease	1	0.25
20	Toxic gastritis	1	0.25
21	Peptic ulcer	1	0.25

TABLE 2 (*a*)—*Incidence of Gastrointestinal Disorders Giving Rise to Anemia in* 1950.

Disease.	No. of cases.	Percentage.
Ankylostomiasis	26	43.33
Chronic diarrhea	16	26.67
Giardiasis	6	10
Cancer stomach	2	3.33
Cancer colon	2	3.33
Colitis	2	3.33
Tuberculosis of abdomen	5	8.33
Peptic ulcer	1	1.67
Sprue	1	1.67
Ascariasis	1	1.67
Amebiasis	1	1.67
Hematemesis of undetermined aetiology	1	1.67

TABLE 3.—*Incidence of Signs and Symptoms.*

Symptoms.	No.	Percentage.	Physical Signs.	No.	Percentage.
Diarrhea	204	51	Tenderness in abdomen	145	36.25
Weakness	178	44.5	Signs in the heart	98	24.25
Pain in abdomen	162	40.5	Congestion in lungs	86	21.25
Fever	116	29	Enlarged spleen	72	18
Loss of appetite	80	20	Enlarged liver	67	16.75
Cough	76	19	Oedema on feet	67	16.75
Dyspnea	68	17	Parrot beaking of nails	65	16.25
Mucus in stools	68	17	Fluid in abdomen	46	11.5
Swellings on legs	68	17	Ulcers on tongue	38	9.5
Blood in stools	54	13.5	Lump in abdomen	33	8.25
General anasarca	46	11.5	Congestive heart failure	18	4.5
Pallor	44	11	Wasting	17	4.25
Constipation	32	8	Neurological signs	12	3
Palpitation	29	7.25	Stomatitis	19	4·75
Vomiting	28	7	Jaundice	8	2
Pain in body	26	6.5	Koilonychia	9	2.25
Indigestion	24	6	Enlarged glands	10	2.5
Distension of abdomen	18	4.5			
Abdomen	18	4.5			
Numbness and tingling	10	2.5			
Headache	8	2.0			
Jaundice	4	1			
Hematemesis	7	1.75			
Dysphagia	4	1			
Itching of the body	3	0.75			

TABLE 4.— *Sex Incidence*

Sex.	No. of cases.	Percentage.
Male	255	63.75
Female	115	28.75
Children (Below 12 yrs.)	30	7.5

TABLE 5.—*Incidence According to Age.*

Age Group.	No. of cases.	Percentage.
10—20 years	11	18.33
20—30 years	19	31.67
30—40 years	17	28.67
Above 40 years	17	28.33

TABLE 5 (*a*).—*Incidence According to Degree of Anemia.*

R.B.C. count in millions/c.mm.	No. of cases.	Percentage.
3.0 to 3.5	107	26.75
2.0 to 3.0	160	40.0
1.0 to 2.0	101	25.25
Below 1.0	32	8.0

TABLE 6.—*Type of Gastric Acid Response.*

Gastric Hydrochloric Acidity.	No. of cases.	Percentage.
Normal	35	22.4
Hypochlorhydria	33	21.2
Achlorhydria	52	33.3
Hyperchlorhydria	36	23.1

TABLE 7.—*Diet Habits.*

Type of diet.	No. of cases.	Percentage.
Vegetarian	44	73.33
Mixed diet	16	26.67
Group (*a*) Rich diet	0	0
,, (*b*) Moderate diet	8	16.7
,, (*c*) Poor diet	52	83.3

TABLE 8.—*Types of Anemia.*

Type of anemia.	No. of cases.	Percentage.
Macrocytic hyperchromic	11	18.33
Macrocytic hypochromic	9	15
Normocytic normochromic	4	6.67
Normocytic hypochromic	14	33.33
Microcytic hypochromic	22	46.67

SPRUE

Out of the 400 cases, 16 (4.0%) were of sprue. Cases of this melody are not seen frequently in this part of the country, but are very commonly seen in Central and Western India. These patients are usually admitted for one or more of the following symptoms :—Chronic diarrhea, wasting, glossitis and anemia. The pathogenesis of anemia in this malady is rather complex and is said to be due to certain factors operating in combination or alone. The diarrhea produces anemia due to mal-absorption of the hematinic principles; a low hydrochloric acid response of the stomach hinders the absorption of iron ; the absence of the intrinsic factor, even in the presence of free hydrochloric acid, as demonstrated by Castle and Rhoads[1], produces a macrocytic anemia ; and according to Stannus[3] failure of phosphorelation leading to a loss of phospholipids, are some of the factors responsible for the production of anemia. The anemia may not be evident until the disease has been established for some time. The intitial blood picture may show a microcytic hypochromic anemia but soon it changes to macrocytic variety. The colour index may be less than one because of iron deficiency. The red cell count is near about 2 millions/c.mm., the mean cell volume and mean cell hemoglobin increase, while the mean cell hemoglobin count and saturation index are variable and the red cells show anisocytosis vacuolation, poikilocytosis and sometimes basophilic stippling; immature red cells may also be seen. The response to treatment in macrocytic anemia is better than in normocytic variety. The response is observed after parenteral liver extract or folic acid therapy.

Case 8.—A. D., a 50 year old female, was admitted on 8-4-50 for loose stools, 10-20 a day, containing mucus, of one year's duration, starting after her pilgrimage to Badrinath. She also complained of pain in the abdomen, flatulence, sore tongue anorexia and weakness. Objective examination revealed emaciation, anemia, parrot beaking of nails, raw beefy tongue and tenderness in the umbilical and epigastric regions. Heart sounds were feeble and a hemic murmur was present in all areas. Stools were frothy and bulky and contained mucus and pus cells. The fat content of the stools was 48 per cent with 38 per cent and 10 per cent as the split and unsplit fat, respectively. Gastric analysis showed achlorhydria, the red cell count was 2.29 millions/c.mm. Hemoglobin 10 Gm. per 100 cc., mean cell volume 134 c u*., mean cell hemoglobin 43 rr., mean cell hemoglobin count 31 per cent, white cells were normal, the general blood picture showed macrocytosis, poikilocytosis, anisocytosis and polychromasia. The blood calcium was 8.8 mg. per 100 cc., and blood proteins 5.6 Gm. per 100 cc. The bone marrow showed a megaloblastic reaction. She was given only curd and bananas to eat, sulphaguanidine, acid hydrochloric dilute with meals and folic acid 16 mg. intramuscularly on alternate days. She felt better with this treatment, the sore tongue cleared up, diarrhea ceased and at the end of the second week the blood showed red cell count 4.4 millions/c.mm. Hemoglobin 12 Gm. per cent, mean cell volume 84 c.u*., mean cell hemoglobin 27 rr., and mean cell hemoglobin count 30 per cent.

Comments :—This patient started a diarrhea after going to Badrinath, which is a common history found in Hill diarrhea progressing on to sprue. The anemia in these cases responds very well to the administration of hydrochloric acid and folic acid together with antiseptics for the intestinal tract, *e g.*, sulphaguanidine and curd.

GASTRIC CARCINOMA

Only 4 cases of gastric carcinoma were admitted to our medical wards. Gastric carcinoma is said to be one of the commonest malignant tumours of the body. The mechanism of production of anemia in these cases is very complex and any form of anemia can occur in these cases. A microcytic hypochromic anemia may be seen due to acute or chronic hemorrhage, deficient intake and poor absorption due to anorexia and achlorhydria, and toxic depression of the bone marrow due to secondary infection of the stomach. The macrocytic anemia may be due to deficiency of the intrinsic factor caused by the destruction of the gastric mucosa, deficiency of extrinsic factor due to anorexia or due to hepatic metastasis, and a normocytic anemia of the aplastic variety may result from metastasis in the bone marrow. The treatment of anemia in gastric carcinoma has not been properly studied because of the attention of the observers to the primary condition. In macrocytic anemia a response may be obtained to parenteral liver extract therapy. Hypochromic anemia responds well to irion therapy, but if the anemia is microcytic without hypochromia, response to iron is very poor. Gastric lavage does some good in iron absorption by reducing the gastritis and toxemia.

Case 9.—A. L., a 50 year male, was admitted on 29-11-49 for nausea, lump and pain in the abdomen, anorexia and emaciation of 6 months duration. On examination he was found to be weak, emaciated and anemic. A hard nodular and tender lump of the size of an egg was palpable in the epigastric region. The stool examination showed occult blood; gastric analysis revealed achlorhydria and blood in all the specimens. The blood showed a red cell count 2.88 millions/c.mm. Hemoglobin, 10 Gm. per cent, mean cell volume 104 c.u*., mean cell hemoglobin, 34 rr., and mean cell hemoglobin count 33 per cent ; white cells were within normal limits. X'Ray examination. after barium meal, showed a filling defect at the greater curvature of the stomach. He was given ferri et ammon. citras gr. 90 daily and 2 cc., liver extract, intramuscularly, on alternate days. Exploratory laparotomy revealed a cancerous growth involving the stomach, colon, glands and liver. After 4 weeks of treatment the red cell count was 3.02 millions/c.mm. Hemoglobin 10 Gm. per cent, mean cell volume 110 c.u ., mean cell hemoglobin 33 rr., and mean cell hemoglobin count 32 per cent.

Comments :—The case did not respond to oral iron and parenteral liver extract therapy as far as his anemia was concerned and this is perhaps due to some depressing effect on the bone marrow.

GIARDIASIS

The giardial infection has been considered to be non-pathogenic, but in this study of 400 cases, 29 were of diarrhea due to *Giardia intes-*

tinalis. They were usually admitted for diarrhea, pain in the abdomen, and weakness and sometimes tenesmus and griping. Most of the cases showed a macrocytic hyperchromic anemia but a hypochromic anemia was also observed. Gastric analysis usally showed a hypo-acidity. Cases showed a good response to mepacrine and the anemia improved after folic acid or liver extract therapy in macrocytic anemia, and to iron in microcytic hypochromic anemia, while the administration of hematinic principles did not bring about any improvement till the *Giardia intestinalis* infection was eradicated.

Case 10.—R. G., a 22 year old Hindu female, was admitted on 8-3-50 for diarrhea, anorexia, loss in weight, ulcers in mouth and occasional fever of 4 months duration. On examination she showed anemia, weakness, parrot beaking of nails, raw beefy tongue and stomatitis. Auscultation of the heart revealed a hemic murmur in all areas. Stool examination showed active forms of *Giardia intestinalis*; blood examination showed a red blood count of 0.9 millions/c.mm., hemoglobin 4.0 Gm. per cent., mean cell volume 150 c.u*., mean cell hemoglobin 44 rr., mean cell hemoglobin count 28 per cent; general blood picture showed macrocytosis, poikilocytosis, anisocytosis and vacuolation. The white blood cell a count was 3400/c.mm. The bone marrow showed a megaloblastic reaction. Giardiasis was successfully treated with mepacrine and she was given 8 injections of liver extract 2 cc .each on alternate days. After 2 weeks the blood picture was red blood count 1.6 millions/c.mm. Hemoglobin 6 Gm. per cent, mean cell volume 144 c.u*., mean cell hemoglobin 37 rr., and mean cell hemoglobin count 29 per cent. She was next given folic acid 15 mg. parenterally on alternate days and after 3 weeks the glossitis and stomatitis disappeared and blood examination revealed red cell count 2.8 millions/c.mm. Hemoglobin 9 Gm. per cent, mean cell volume 114 c.u*., mean cell hemoglobin 32 rr., and mean cell hemoglobin count 28 per cent.

Comments :—This case of giardiasis showed a macrocytic hyperchromic anemia. The response to liver therapy was rather poor and a better response was observed after folic acid therapy.

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MEDICAL PRACTICE

EXPERIMENTAL AND CLINICAL STUDIES ON THE USE OF TERRAMYCIN* IN ACUTE PERITONITIS

A PRELIMINARY REPORT

K. N. Udupa,† and Jal Lal,‡

Acute peritonitis, produced by infections or perforations of the various abdominal viscera, was one of the most dreaded diseases during the pre-chemotherapeutic era of Medicine, resulting almost uniformly in death. Several factors are responsible for the advancement of the present day therapy which usually results in complete recovery of most of these patients. Amongst them, discoveries of many of the newer broad spectrum antibiotics such as aureomycin, terramycin, *etc.*, and also the better understanding of the various general supportive measures, are of utmost importance. The latter problems have been thoroughly discussed by Coller and Ransom[1] in their classical chapter on "the treatment of peritonitis and peritoneal abscesses", and one who is interested in these problems should refer to their original paper.

A large number of investigations were carried out in recent years to find the best antibiotic for treating this condition. Since acute peritonitis is an infective condition caused by a mixture of organisms such as streptococci, *B. Coli*, *Clostridium welchii*, *etc.*, an ordinary antibiotic, which has a limited action on certain groups of bacteria only, will have not much value in the treatment of this condition. Thus Zintel *et al.*[9] recently studied in experimental animals the comparative value of the sulphonamides, penicillin and streptomycin, either individually, or in combination, and came to the conclusion that amongst these three, penicillin alone was the antibiotic of choice for controlling infections of this nature.

On the other hand Yeager *et al.*[7] and quite recently Udupa[5] studied the comparative value of penicillin, aureomycin and chloromycetin in acute peritonitis of both experimental and clinical origin, and all of them came to conclusion that aureomycin alone was the best antibiotic for this purpose. However, in a large series of 235 cases of acute peritonitis treated by aureomycin alone, Wright *et al.*[6] have reported a mortality of 3.7 per cent.

Since the discovery of another broad spectrum antibiotic, namely, "Terramycin," in 1950, various claims have been made for this drug in curing acute peritonitis. Pulaski[3] *et al.* found its great efficacy, with a dramatic response, in all of their 10 patients suffering from this condition. They also obtained similar good results in peritonitis of experimental origin. Similarly, Yeager *et al.*[8] have also observed good and rapid recovery in all of six patients stricken with acute septic peritonitis, by the use of terramycin alone. Their experimental study also supported their experience in the clinical cases. From the prophylactic point of view, Dearing and Needham[2] studied the efficacy of terramycin as an antiseptic on the intestinal flora of a large number of patients undergoing bowel operations, and found that it has a remarkable power of producing an almost ideal antiseptic action in all the patients so studied. In order to evaluate these various claims made by several investigators and studied from different angles, the present investigation was carried out by both of us in experimental animals and clinical cases. Our methods of investigation and the results obtained are briefly given below :—

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MATERIALS AND METHODS

(*A*) *Experimental* :

We closely followed the Zintel's[9] method for production of experimental peritonitis in dogs and our methods have been described in detail by Udupa[5] in one of his recent papers. Briefly, they consisted of the following :—Dogs of both sexes were selected. Under open ether anesthesia the abdomen was opened by a paramedian incision observing all the aseptic technics and precautions. The conical tip of the cecum, which almost resembles the human appendix, was then isolated and brought out. It was then tied at its base with a silk ligature after isolating and cutting its blood vessels. An incision of about 2" in length was made distal to the ligature, taking every precaution not to allow fecal matter to contaminate the abdominal wound. Then the tip of this opened and avascularised appendix was held in a hemostat and made to contaminate the whole of the peritoneal cavity by taking it around in an anti-clockwise manner from the left to the right hypochondrium and downwards. The abdomen was closed in layers using silk sutures and a dressing was applied. Immediately after this, 50 cc. of castor oil ws given through a stomach tube for increasing the peristalsis of the intestines, so that the infection produced by the above experiment might become widespread. Thus a condition was produced in the experimental animal which is almost identical to that of acute peritonitis produced by a perforated appendix in human beings. Usually, all these dogs regained consciousness within two hours and started drinking fluids offered to them. However, no intravenous saline or other fluids was given to any of them by way of supportive treatment. Those dogs that survived more than 8 hours after the operation, developed typical acute diffuse peritonitis.

Five dogs in all were selected for this experiment. Two were used as controls and three for the use of terramycin. The latter drug was given by mouth in capsule form in the dosage of 25 mg. per kilogram of body weight four times a day till the temperature touched the normal level. No bacteriological studies were made along with these experiments in view of the uncertainty of their value in these experiments as already reported by Zintel *et al.*[9] Only the clinical manifestations such as temperature, pulse, *etc.*, have been carefully recorded.

(*B*) *Clinical* :

So far we have used terramycin hydrochloride as a therapeutic agent in two patients both suffering from acute diffuse peritonitis. One was the result of an acute perforation of a gastric ulcer, and the other a perforated appendix. The first patient was operated upon after 18 hours, and when his abdomen was opened, we found all the signs of acute diffuse peritonitis with an accumulation of a large amount of purulent fluid in the whole peritoneal cavity. The pus was aspirated and the rent in the stomach was sutured. The abdomen was closed after placing a drainage tube. Terramycin was given intravenously for the first three days with a dosage of 1.5 Gm. followed by oral terramycin for the next six days with dosage of 2 to 1.5 Gm. in 24 hours. The second patient was operated upon after 16 hours of the onset of her symptoms, and when the abdomen was opened, gangrene of the appendix with perforation and acute diffuse peritonitis with pus all over the peritoneal cavity were detected. An appendicectomy was performed and all the pus was mopped up. The abdomen was closed in the usual manner without a drainage tube. Terramycin was given intravenously for the first three days and then by mouth with the same dosage as in the first case, till the patient completely recovered from her illness. The detailed case histories of these pateints will be given later on.

In addition to this, two more patients, who had to undergo some operations on the colon, received terramycin by mouth as a prophylactic agent to produce maximal intestinal antisepsis. Of these, one had a right hemicolectomy, and the other had an iliotransverse colostomy, both for iliocecal tuberculosis. Both these patients received two capsules of 250 mg. each, three times a day, totalling 1.5 Gm. in 24 hours, for three days before and for about five days after the operations. No other antibiotics were given to them in any other form during the course of these surgical treatments.

RESULTS

(*A*) *Experimental* :

Out of 5 dogs, the two which were used for control purposes died within 24 hours. At autopsy, both these dogs wre found to be suffering from acute diffuse peritonitis. There were collections of a large amount of seropurulent fluid and gas in the peritoneal cavity. This observation is in conformity with our previous experience reported by one of us (K. N. Udupa[5]) in which all the four control dogs died of acute peritonitis within 1 to 5 days. The other three dogs of this experiment, who received terramycin by mouth 2 to 4 hours after the operation, recovered completely and uneventfully within 7 to 12 days. All of them became active within 3 days and we did not notice any special toxic symptoms, which could be attributed to the drug, in any one of them.

(B) Clinical :

Our results in the clinical cases would be well shown if brief histories of the cases with progress reports are given and hence these are reproduced below :

CASE REPORTS

Case 1.—Mr. S., aged 42 years, was admitted to the Civil Hospital, Mandi at about 9-30 p.m. on the 5th September, 1951, with a complaint of sudden onset of acute pain in the upper abdomen at about 4 p.m. that day. The pain was at first limited to the epigastrium, but later became diffuse all over the abdomen. He had had a fairly heavy meal about two hours before the onset of pain, and was on his way home when he was suddenly caught with this excruciating pain. The agony was so much in the beginning that he fainted for a while on the road side. When he was admitted to the hospital about 5½ hours later the upper abdomen was found very rigid and tender. however, the lower abdomen was not much tender. Except for the pain, the general condition of the patient was fairly satisfactory, with a temperature of 99.0° F. and a pulse rate 96 per minute. The Medical Officer on duty, who examined him at that time, did not find it necessary to open the abdomen immediately, thinking that it might be a simple biliary colic. However, a possibility of perforated peptic ulcer, and acute pancreatitis was also kept in mind. After the administration of a a few sedatives, his pain became comparatively much less during the night. The next morning, when the patient was examined by us, we felt that he had already developed acute diffuse peritonitis and therefore a laparotomy was immediately performed.

On opening the abdomen under open ether inhalation anesthesia, the whole abdominal cavity was found to be filled with seropurulent fluid , and there were all the signs of acute diffuse peritonitis. A few food particles were also seen floating in the pus. Hence our attention was immediately directed to the stomach, where we found a rent of 1 cm. in diameter in the pyloric region of the stomach. This perforation was then closed in the usual manner by placing three catgut sutures over a free omental graft and the abdomen was closed after aspirating all the pus from the cavity and placing a drainage tube through a separate stab wound.

Further Course and Treatment :—

(1) A Ryle's tube was passed into the stomach and intermittent suction was maintained throughout the period of his acute illness *i.e.*, for about four days.

(2) Morphia 1/6 gr. was given subcutaneously every 6 hours for the first four days.

(3) About 3,000 cc. of fluid in the form of normal saline and glucose solution was given intravenously by the drip method for the first three days and later on partially by mouth and the rest by the intravenous route till he started taking his normal diet by mouth. In addition to this, an equal amount of fluid to that aspirated from the stomach was replaced *via* the intravenous route in the form of normal saline.

(4) Fowler's position was maintained throughout the period of illness.

(5) *Antibiotics* :—From Figure 1, one can see that for the first three days he received terramycin 1.5 Gm. intravenously by the drip method and from the fourth day onwards he received terramycin by mouth in capsule form, 2 Gm. per day for the next three days, followed by 1.5 Gm. for another three days.

With these measures he made an uneventful recovery in nine days. (See Fig. 1) Even from the fourth day onwards he ws found very cheerful and appeared to be completely out of danger. He had no special toxic symptoms from this drug except a slight thrombophlebitis at the site of intravenous injection. He was discharged from the hospital on the twelfth day.

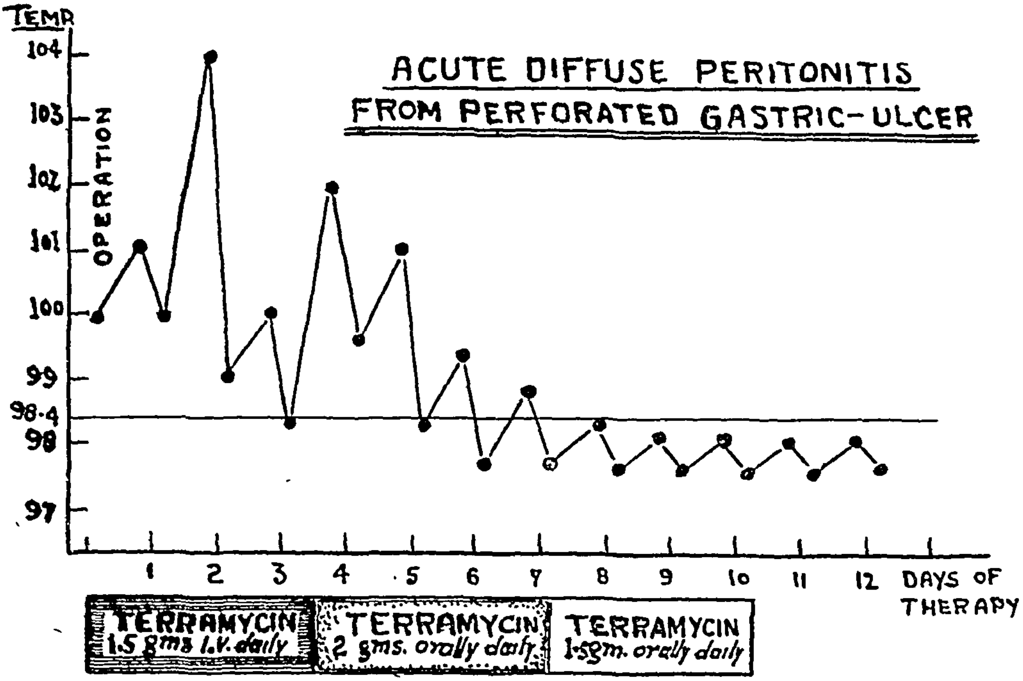

Fig. 1. Case No. 1 Mr. S 42 Years

Fig. 1.—Temperature chart of Case 1, who developed acute diffuse peritonitis from perforated gastric ulcer. He made uneventful recovery with the use of terramycin the only chemotherapeutic agent employed.

Case 2.—Mrs. P., aged 43 years, was admitted to the Civil Hospital, Mandi, at 8 a.m. on 19-9-51, with the chief complaint of acute pain in the abdomen and vomiting for about two hours. She informed us that the pain first started in the umbilical region, but soon after became diffuse all over the abdomen. She also gave the history that she had three or four similar attacks prior to this one. On examination, she looked fairly ill, but taking into consideration her previous history it was decided to watch her for a few hours. By 8 p.m. on the same evening, the general condition deteriorated much, with an increased pulse rate and more frequent vomiting. Now the pain had become more intense all over the abdomen. A probable diagnosis of acute appendicitis was made and a laparotomy was decided upon. On opening the abdomen, 16 hours after the onset of pain, the whole peritoneum was found edematous, and congested. In addition to this, the entire peritoneal cavity was filled with purulent fluid. On aspirating the pus, we found the distal two thirds of the appendix lying free on the brim of the pelvis, gangrenous and with a perforation of 1 cm. in diameter in the middle of it. The proximal one third of the appendix was also found acutely inflammed and edematous. An appendicectomy was performed in the usual manner and the abdomen was closed without any drainage tube.

In the post operative period the same supportive treatment, such as intravenous saline, *etc.*, as mentioned in the first case, was given. Similarly, terramycin was also given in the same manner, *i.e.*, for the first three days it was given intravenously in the dosage of 1.5 Gm. per day, followed by terramycin capsules orally in the dosage as shown in the Figure 2. She completely recovered from her illness in about nine days and was discharged from the hospital on the thirteenth day. She had also developed a mild type of thrombophlebitis at the site of injection which also gradually subsided after a few days. In addition to this, twice in the course of treatment, she had looseness of the bowels for a day each time. However, this was easily remedied by a few doses of bismuth and kaolin powder. Otherwise, she was well and active from the third day onwards, and one could hardly realise by looking at her, that she ever suffered from such a serious disease.

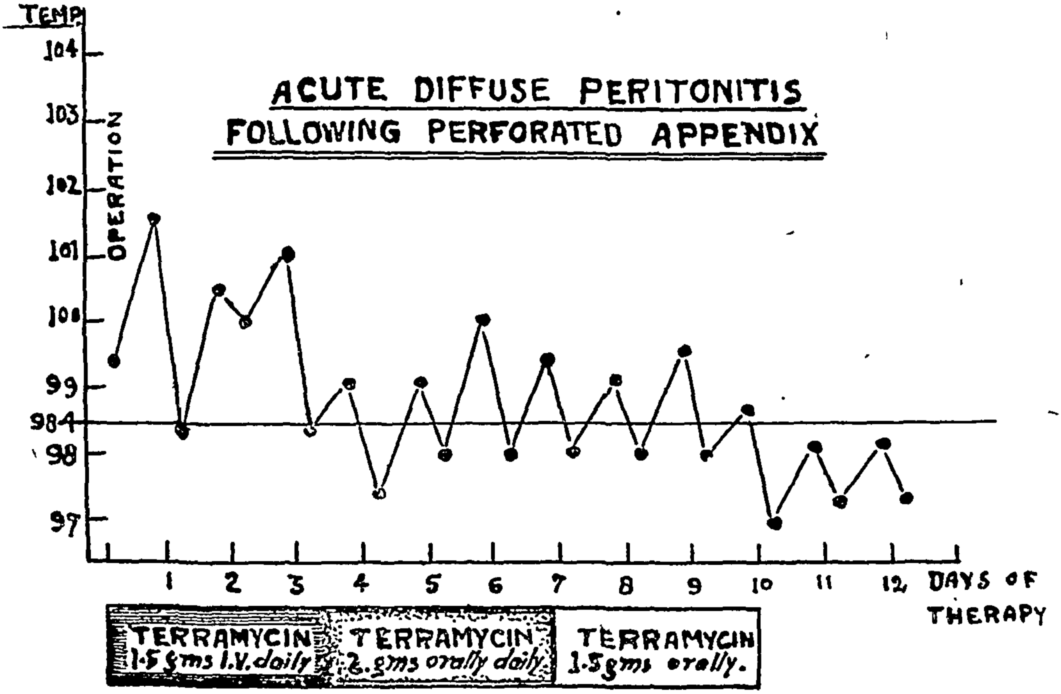

Fig. 2. CASE No. 2 MRS. P. 45 YEARS

Fig. 2.—Temperature chart of Case 2 who developed acute diffuse peritonitis from a perforated appendix. She responded well to terramycin alone and she completely recovered from her illness.

In addition to these two cases, the other two patients, who received this drug as a prophylactic agent, also had a very smooth post-operative course. Neither of these patients developed any temperature, nor did they have any signs of sepsis anywhere. Usually our other patients who did not receive terramycin, and who had undergone similar operations had a rise of temperature upto 101.0° F for at least three to four days, inspite of treatment with sulphasuxidine and penicillin. In these two patients, the temperature rose upto only 100° F. on the first day, followed by an afebrile course for the remaining days. Although one should not draw any definite conclusions from this small series of cases, one is still justified in thinking that the discovery of these newer antibiotics have completely changed the outlook for these patients.

DISCUSSION

It has been reported by most of the previous investigators [2], [3], [4], [8] that terramycin hydrochloride was used effectively in the treatment of many diseases caused by gram-negative and gram-positive bacteria of both aerobic and anaerobic origin, spirochaetes, and also by the amebae. It is readily absorbed from the gastrointestinal tract and is usually well tolerated by patients. Since it is a broad spectrum antibiotic with a very wide range of activity on most bacteria, it is specially useful in diseases produced by mixed infections. An important example of such infections is acute peritonitis, in which all the causative organisms, both aerobic and anaerobic, like streptococci, *B. coli*, *Clostridium welchii*, *etc.*, are very susceptible to this drug. The only organism of the intestinal canal which is not affected by this drug is the *Bacillus proteus*, which, incidentally, is not a pathogenic organism. Hence this drug is found effective not only in the fulminating acute diffuse peritonitis as a therapeutic agent, but also as a prophylactic agent in preventing the development of peritonitis in cases where it is likely to develop, *e.g.*, after operations on the colon and rectum. In this respect, its action closely resembles that of aureomycin.

Amongst the toxic effects, nausea, vomiting, and diarrhea have been reported to occur in some cases by the oral use. In none of our patients, nor in our experimental animals did we observe any such toxic symptoms. However, one of our patients with acute diffuse peritonitis did develop looseness of the bowels twice in the course of her stay in the hospital. Even this remained for a day only, each time, and was easily relieved. It has also been observed by us that these patients are liable to develop symptoms of vitamin B complex deficiency, probably due to the destruction of all types of bacteria, both pathogenic and non-pathogenic, from the intestinal tract. Hence a course of vitamin B complex therapy, immediately after the completion of the antibiotic therapy, was also given to our patients with remarkable improvement in their general conditions.

By the intravenous injection of terramycin, the common toxic manifestation has been the development of thrombophlebitis at the site of injection. Even this disappeared of its own accord in due time. To avoid its development, the drug should be injected as dilute as possible, preferably in the concentration of not more than 5 mg. per cc. Usually a vial containing 500 mg. is dissolved in at least 100 cc. of normal saline and is injected through a big vein, as slowly as possible. Further, it is also stressed that the intravenous injection should be given only if it is very essential, and as soon as the oral method can be adopted, the latter route should be employed.

By adopting these methods of treatment and precautions, we are well satisfied from our experience in a small series of experimental animals and patients, that terramycin is one of the most useful drugs ever discovered for controlling acute diffuse peritonitis, as well as in preventing the development of peritonitis in colonic surgery. In this context, Pulaski ana Shaeffer[3] have laid down certain criteria that the best antibiotic for a specific disease must have the following qualities :—

(1) It should be rapidly effective.
(2) It should be of relatively low toxicity.
(3) It could be given to the patients with ease.
(4) The cost of the drug should be low.

Almost all the qualities are present in terramycin when it is used as an antibiotic in acute peritonitis. However, there may be one objection to its free use in this condition, namely, its excessive cost in comparison with many of the other cheaper agents like penicillin. But, by adopting this latter drug for treatment there is always a risk of increased mortality and morbidity. Besides, the total cost of penicillin injected over a long period and the total stay of the patients in the hospital with its attended expenditure, if added together, the diff rence in the cost of the two treatments becomes almost negligible. Therefore, we feel that the free use of this better antibiotic should be made in the treatment of peritonitis to ensure a safe and rapid recovery.

SUMMARY

(1) The recent discovery of many of the broad spectrum antibiotics, especially aureomycin and terramycin, has completely changed the outlook for patients suffering from acute diffuse peritonitis.

(2) Five experimental animals in all were used for this investigation. Out of these, 2 were used as controls for the development of acute peritonitis, and both died within 24 hours. The remaining three, who also developed acute peritonitis by the experimental procedure, received terramycin, with a dosage of 25 mg. per kilogram of body weight by mouth, and to our surprise all of them survived.

(3) Two patients with acute diffuse peritonitis, the result of perforated gastric ulcer and a perforated appendix, were treated by terramycin, at first intravenously for three days, and then orally for six days, with a dramatic response in both the patients. In addition to this, two patients undergoing surgery of the colon received terramycin as a prophylactic agent with a very smooth post-operative course.

(4) Since its efficacy is great, administration is easy, and toxic effects are negligible, it is the best antibiotic for treating acute peritonitis.

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* The Terramycin used in these studies was kindly supplied by Dr. Ray A. Patelski of Chas. Pfizer & Co., Inc. Brooklyn, 6, New York, U.S.A. The authors are greatly indebted to the above firm for the generous gift of this drug.

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CASE REPORT

WATERHOUSE - FRIDERICHSEN SYNDROME

REPORT OF A CASE

M. M. Rananavare. *

The Waterhouse - Friderichsen syndrome is characterised by symptoms of sudden circulatory failure as a result of extensive bleeding of the adrenals on both sides. This is preceded by un-characteristic complaints such as fatigue, abdominal pain, subcutaneous petechial hemorrhages and high fever. In the majority of cases the meningococcus has been the causative organism though the clinical picture of meningitis is not an invariable accompaniment.

The following case report greatly simulates the above syndrome with few variations from the classical picture.

CASE REPORT

Clinical History :—On the 28th September, 1951, a 24 year old American lady was admitted to the Sassoon Hospital, in a collapsed state with the complaints of hematuria, pain in the kidney region and subcutaneous petechial hemorrhages. A few days earlier, she had a swelling of bluish discolouration over the right calf muscles. She had been taking 'Temparin' tablets by mouth on the advice of the family doctor who probably diagnosed the condition as thrombophlebitis. A day earlier, she had passed a moderate amount of blood in the urine, following which she had felt giddy and weak.

She gave a history of a tendency to form hematomata on the "slightest" injury, and a history of a "kidney chill" two years previously. On physical examination, she was conscious and said that she felt a lump in the throat. The mucous membrances were very pale. There were several subcutaneous petechial hemorrhages, specially over the extremities. Pulse : 13, rapid and feeble ; respirations : hurried and shallow ; temperature : subnormal ; B. P. 90/40 mm. Hg., bleeding time, 6 minutes, clotting time, over 15 minutes ; platelets were in moderate numbers in the blood smear. Just before death, which occurred within an hour of admission to the hospital. she became extremely pale and pulseless with a small amount of blood at the nostrils and the mouth.

Clinical Diagnosis.—Death due to acute internal hemorrhage.

Autopsy Report :—The body of a white adult woman, well developed and well nourished. A few subcutaneous petechial hemorrhages over the left arm and the right leg ; pupils equal on both sides, hemorrhagic edema over the left fold of the glottis (The patient during life complained of a lump in the throat). Both lungs showed emphysematous bullae and the cut surfaces were pale and dry. The heart. spleen and the liver were soft and pale but not enlarged. A diffuse hematoma was present in the mesentery of the small bowel, but there was no trace of hemorrhage inside its lumen. The kidneys, on both sides, were enveloped in large blood clots. The cut surface revealed blood clots in the pelvis of each kidney (See Fig. 1.) The suprarenals were compressed by the surrounding blood clots. The brain was soft and pale. There was no evidence of meningeal inflammation."

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Microscopic Examination:—"The suprarenals showed irregular necrosis and necrobiosis of whole of the adrenal tissue; hemorrhage and cell infiltration well marked externally; periadrenal vessels thrombosed; no direct continuity between the zone of cortical necrosis and of surrounding hemorrhage." (Fig. 2.)

The liver showed central lobular necrosis due to anoxemia. The kidneys showed cloudy swelling and necrosis of the tubular epithelium.

Autopsy Diagnosis :—Acute perinephric and periadrenal hemorrhage resulting in sudden death.

DISCUSSION

The symptom complex and the post-mortem findings of this case greatly resemble those of the Waterhouse-Friderichsen syndrome. The variation from the classical picture is in the etiology of the syndrome. Meningococcal septicemia is absent in this case. A blood dyscrasia, present since childhood, and injudicious administration of an anticoagulant may have caused severe bleeding around the adrenals.

Golden's [2] conclusions on examination of the cortical lesions of the adrenals in a variety of diseases in man, and in diphtheritic and in malarial infections in experimental animals, are as follows :—

1. Necrosis of the adrenal cortical cells exists as a pathologic entity and takes the form of simple, coagulative or anemic necrosis which is followed in time by mild leucocytic infiltration.
2. Hemorrhagic infiltration into the adrenal cortex is a variant of this type of necrosis. Hemorrhage appears to be produced by diapedesis and is dependent on concomitant destruction of sinusoidal reticulum.

In the case under discussion, it is not certain that the necrobiosis of the cortical cells is the cause of hemorrhage from the adrenals because, microscopically, no direct continuity could be demonstrated between the zones of necrosis and of surrounding hemorrhage. Thrombosis and periadrenal hemorrhage may have led to a cutting off of the blood supply and consequent ischemic necrosis of the adrenal gland.

SUMMARY

The clinical history and post-mortem report of a white woman who died of sudden circulatory failure as a result of severe bleeding around the adrenals on both sides, has been narrated. It differs from the classical Waterhouse-Friderichsen syndrome on the etiological basis, in that, this is a case of blood dyscrasia aggravated by the administration of an anticoagulant.

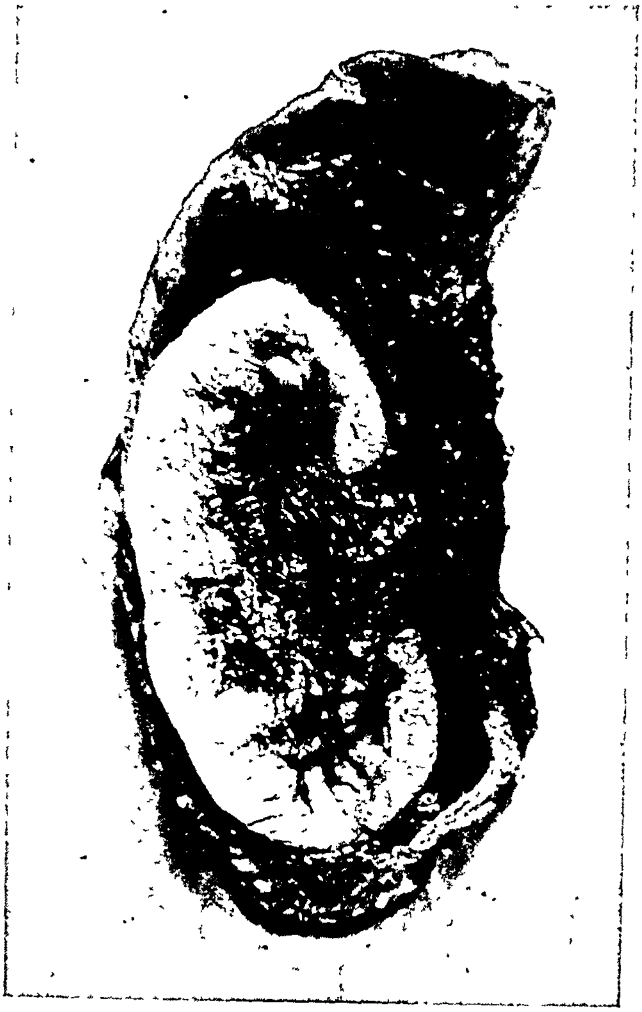

Fig. 1.—Kidney and the suprarenal embedded in the blood clot.

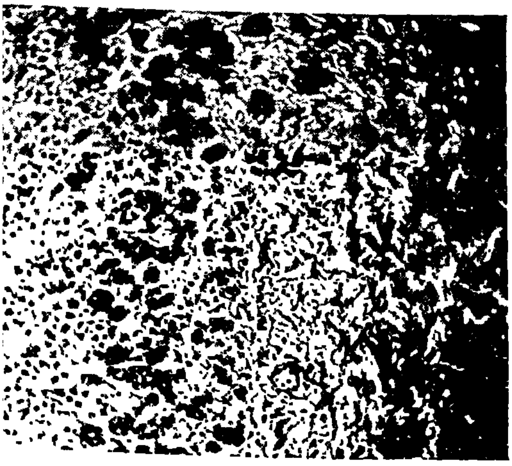

Fig. 2a.—Photomicrograph showing hemorrhage on one side and normal adrenal tubes on the other side.

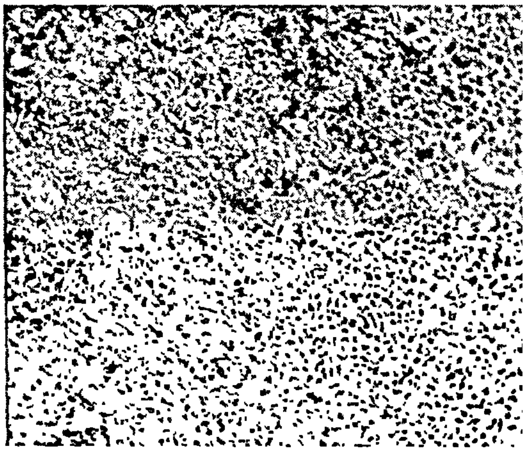

Fig. 2b.—Photomicrograph showing cortical necrosis of the adrenal gland.

ACKNOWLEDGMENT

I am grateful to Prof. P. G. Gollerkiri, M.D., and Drs. R. V. Junnarkar and Mehta for their valuable help in the preparation of this paper.

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MISCELLANEOUS

MEDICINE IN SOVIET RUSSIA

From our staff Correspondent

Under the auspices of the Bombay Medical Union, Dr. A. V. Baliga gave a lecture on medicine in Soviet Russia. He said that the status of Soviet medicine, at present, is very high and it is very necessary that one should compare Soviet medicine as it is today with what existed 33 years ago. Soviet Russia had infectious diseases like typhoid, small pox, malaria, cholera and plague just as we have in India, and they have fought these scourges and also other infections like tuberculosis and meningeal diseases. Typhoid was endemic in Soviet Russia three decades ago. The incidence was 40 per 10,000. By 1930, they had decreased the incidence of typhoid to 8 ; by 1940, 3 per 10,000 and today it is practically stamped out. They overcame water-shortage, built modern sewage systems and had strict sanitary conditions for food products. Small pox was prevalent in Soviet Russia for a long time. It is preventable, and they have shown that it is preventable. By law, the parents are responsible for having their children vaccinated at birth and re-vaccinated at the age of 4—5 and 10—11 and again at 18—20. They have regular and frequent vaccination campaigns. Plague, cholera and typhus were the diseases responsible for severe ravages, but all have been tackled and none of these are seen nowadays. In Soviet Russia, malaria was prevalent as in India, particularly in Caucasus and other parts of the country. After the socialized health services came in, various measures of controlling the diseases were adopted. Formerly, 3—4 million people were affected with this disease but now it has been stamped out completely. The scientific measures adopted were examination of the infected population, prophylactic treatment with quinine and other anti-malarial drugs, eradication of the sources like water collections and mosquitoes, and by health education. They have similarly fought other diseases like diphtheria, scarlatina, as well as infections like tuberculosis and venereal disease. The most important factor that has helped the fighting of the disease is the higher standard of nutrition of the children and grown-ups in the country. The mortality rates of tuberculosis little over 3 decades ago were high. There were few hospitals to minister to the requirements of the people. Owing to the big rise in the specially trained medical personnel and an intensive campaign, both as regards education of the public and isolation of the infected cases, examination of the families and the introduction of B.C.G. (1936) as a prophylactic, tuberculosis in children and in later life is rare. Plenty of fresh air is provided. If you go to a tubercular sanitorium in fair weather, when there is sunshine, you find the inmates in the open for 24 hours. In the winter, they are allowed upto 8 o'clock in the open or in verandahs. In the sanitorium the surroundings are very pleasant and children do not feel that they are away from home. They have huge compounds with pine trees—the reason for this being that the air that blows through the pine trees is beneficial for combating tuberculosis. As for food, milk with cream is given to them, and the way the individual requirements of the children are attended to, even the richest do not get it in our country. Tuberculosis is treated with horses' milk which is rich in vitamins—vitamins which are very much more potent than in any other item of food. Venereal diseases were very common in Russia, the incidence being as high as 186 per 10,000 in urban areas ; in rural areas much less. The incidence of gonorrhea was as much as 125 per 10,000. This problem was tackled on different lines. By propaganda and education of the people, making available all information about the spread of the disease and prevention of the infection, this disease was controlled. Detection of the disease was prompt and all facilities for the treatment of the patient were available free to all the citizens. All attempts to find the contacts and to treat them successfully were also vigorously adopted. This was done not by legislation but by persuasion, by education and by finding out the causes of venereal disease. The main source of infection is prostitution, and they have done away with prostitution not by legislation but by finding out the economic causes and supplying gainful occupation. When a maid or a female clerk, for instance, is dismissed from her job due to unsatisfactory work, this female finds prostitution a convenient way out of her pecuniary problems. In Soviet Russia, all prostitutes' problems are studied and they are sent to an institution where they are given work according to their mental calibre. They have a co-operative society through which their produces are sold and they live happily in such a condition. Even if a young man goes astray, he is retrieved by being given proper chances. In order to cultivate good mental hygiene, plenty of facilities are provided for recreation and relaxation. There are places where physical culture, dancing, painting, dramatics, sculpture are available. Everywhere there are institutions where they can develop their aesthetic attainments. The ambition of a Russian girl is to become a ballerina, and it is considered the highest form of attainment for a woman. Venereal disease has been conquered by gainful occupation of the people, particularly youths, in what they call cultural activities—developing their aesthetic attainments, and in that way, without legislation, they have done away with prostitution and consequently venereal disease. The infant mortality has been reduced very much and that too by health education. Health education has been actively encouraged by the State Govt. in which there has been co-operation of all classes of people particularly the intelligencia. The propaganda for health education is carried out by the press, by radio, by lectures, films and posters, and by mouth. In Soviet Russia as a whole, they attach much more importance to the prevention of the disease than to the curative aspect, and it is for this purpose that health education has been given most priority. Health education is applied with equal zeal in industrial medicine, in the treatment of tuberculosis, in fighting venereal disease or any other infectious disease, and in school hygiene, and they have separate hygiene-physicians and epidemiologists. The physical culture movement is another thing on which they lay great stress, and in the last six years it has spread like wildfire throughout the country. It has become very popular, and people have become lovers of sport. They have found that people who are interested in games have a more healthy outlook on life ; they have good mental health ; their personal hygiene is improved and their outlook on their daily work is changed. The mass drills and exercises infuse intense self-pleasure in people. They are aware that all these things go a long way in altering the atmosphere in which they live.

Rest Houses and Sanitoria. In 1913, there were not more than 10—15 rest houses in the country. In 1940, 6 million were taking advantage of such places. Rest houses are used by the people for recuperation of their health after operations or after a period of heavy work. There are also sanitoria for tuberculosis as well as for health resorts. The old palaces of nobles and czars have been requisitioned for such purposes ; a number of new ones have been built for the same purposes. It is in these places that a number of workers spend their earned leaves, which is compulsory. There is also a practice that the whole factory closes down for a month and they go for a change.

Dr. Baliga spent 6 days in a rest house in Kazrasthan. The people of this place look and behave similar to Indians. Their customs, e.g., embracing, resemble ours. Facilities for enjoyment in such a place were described by him.

In Soviet Russia, there is no private practice for a doctor. Health services are conducted by the State. Everyone gets free medical attention, and the State spends twenty-five per cent of its revenue on the health of the people. Their system of health services is better than in England and Sweden. They now have 200,000 doctors as opposed to 20,000 in 1913. The number of hospital beds have increased eight-fold, maternity beds about forty times and nurseries hundred times. They have polyclinics like an out-patient department of our general hospital, working in close cooperation with their hospitals. Most of the investigations are carried out in the polyclinics. Each general hospital has a large staff. He thought it was a joy to live and work in such a hospital. The hospitals for children are very well looked after and their life is made extremely pleasant with individual attention. Children are wheeled out and kept in the open ; their individual tastes are met with.

For infectious diseases like diphtheria and scarlet fever, they have the 'box' system whch is airtight so as to prevent the spread of infection. Doctors and nurses have to change their uniforms when they get in and out of such a box. In Moscow, they have a hospital with 40 beds for normal children, where they study the normal growth during this period. Nowhere in the world is there such an arrangement. People with chronic illnesses, heart disease and paralysis are visited in their own houses daily by doctors.

Pregnant women are given special antenatal and postnatal facilities. She is given five weeks' leave before confinement and six weeks' leave after confinement with full pay. During her pregnancy period, she is given light work and an extra free ration of important articles like milk, and an extra ration of clothing, blankets, etc. The mother is given time off to nurse her child if she is employed.

As Dr. Baliga is interested in surgery, he spent most of his time in attending surgical work and found surgery, both major and minor, of a very good order. He has seen big operations like resections of the lung and stomach and pulmonary artery being done with ease and perfect efficiency. In an operation theatre, the whole unit works as a team. Nurses are trained and the doctors have not to shout for the instruments as there is good anticipation on the part of the members of the staff. He attended a few clinics in neuro-surgery and saw the method of evaluation of a case of brain tumour by a neuro-physician, neuro-ophthalmologist, neuro-otologist, neuro-psychiatrist and neuro-surgeon. He heard the critical discussion and method of diagnosis. Nothing is taken for granted. In such a unit, 5 or 6 operations on brain tumour are performed everyday. Their failures of diagnosis are also discussed and they are not afraid of losing their reputation. He saw a unit working on the diagnosis of cerebral tumour by examination of the cerebrospinal fluid alone, staining with a particular technique and to be examined by a luminiscent microscope; but this work has not yet been published. They have made great strides in anaesthesia. Most of their operations, including major operations, are done with local anaesthesia like block anaesthetics. Local anaesthesia is given to all except children below six. A great advantage of this method is that the patient's co-operation is available and there is absence of shock, hence transfusions like that of blood are hardly used.

They prevent post-operative complications by judicious exercises in which the patient is trained before the operation. They have made a study of the action of muscles in various parts of the body and the patients are made fit before operation for the prevention of complications. They have made great strides in experimental surgery and they have attempted trasplantation of lungs, heart and limbs in dogs.

In medical colleges, there is a teacher for every 6 students. 90 per cent of the students get stipends from the State and 95 per cent of them pass their examination at the first attempt. Examinations are held every 3 months, and those who fail are weeded out if they are found unsuitable for the medical course. Some who are backward are given special tuitions.

He also attended the Convocation of the Second Medical Moscow Unit, where 720 students graduated. It was unceremonious—no gowns were worn—there were no processions. There were few simple speeches by the Professor, by the Head or representative of the Health Ministry and a reply by one of the successful candidates. 18,000 doctors pass out every year. There are facilities for a Refresher Course and every 3rd year they must attend the same. They are paid in full during their attendance at the Refresher Course.

Research work is carried out in 300 institutes. Medicine cannot develop where there is no science. That is lacking in our country. India is nowhere on the research map of the world. Research is carried on by everyone in Soviet Russia, at least two hours a day being devoted to research. That is one of the several reasons why medicine is so far advanced in Soviet Russia. Researchers are highly respected and paid.

In the course of answering the questions put to him, Dr. Baliga added that there are very many women doctors in Soviet Russia—about 62 per cent. Many of them are pediatricians, because they are kinder and more sympathetic than men. The women get married early, at the age of 18 to prevent promiscuity. Six per cent of the revenue of every factory is set apart for health amenities. The trade unions, too, subscribe. Medical education took 5 years till 1945, but owing to the poor standard of the graduates, the course was increased to 6 years. At least one foreign laguage was compulsory. The average doctor knows German, French or English. Those who do the 'Feldschers' Course, which is a 3 years course, are classified as auxiliaries. Records of patients in the hospitals are very well kept, in chronological order in duplicate : one with the Ministry and one with the patient. Their medical history is kept beautifully from the womb to the tomb.

THIRD ALL-INDIA CONFERENCE OF INDUSTRIAL MEDICINE

IMPRESSIONS OF A CORRESPONDENT

The third All-India Conference of Industrial Medicine was held in Bombay on the 13th, 14th and 15th December, 1951 at the Seth G. S. Medical College, Parel, Bombay, under the auspices of the Society for the Study of Industrial Medicine.

The first two conferences were held at Jamshedpur, the birth-place of the Society.

More than 100 delegates and members attended the third All-India Conference. The proceedings of the Conference were inaugurated by the Hon'ble Dr. M. D. D. Gilder, Minister for Health, Bombay State, who traced the history of industrial medicine and recalled the time when industrial physicians used to be Certifying Surgeons. Dr. Gilder hoped that the scope of industrial medicine would be extended not only to the employees, but to the employees' dependants and also to small industries or small establishments like shops which, by ordinary comprehension, cannot be classed as industries.

Dr. J. C. Patel, while welcoming the delegates, suggested to the Government the establishment of an industrial health council for the co-ordination of medical benefits to industrial workers. He also suggested that a diploma in industrial medicine may be started for the benefit of those employed in industry and future recruits. He further suggested a co-operative hospital should be started in Bombay by a group of industries.

Dr. J. R. Kocchar, the President of the Society, traced the history of industrial medicine and compared the present state of industrial medicine in India to that existing in countries like England or America.

Messages wishing the Conference success and goodwill were received from various Ministers and Governors.

Dr. H. P. Dastur declared the exhibition open—an exhibition on industrial medicine and safety devices. The exhibition was mainly organised in four sections : (1) by the Labour Department of the Govt. of India, (2) Tata Industries, (3) Tata Iron & Steel Co. Ltd., Jamshedpur and (4) Lever Brothers (India) Ltd.

A number of posters, safety devices, and medical literature on industrial medicine were exhibited.

The Industrial Exhibition was of great benefit to the delegates, so much so, that some of them sent a number of officers from their firms to see the exhibits, safety devices and charts reducing the number of industrial accidents. The exhibition was largely patronised by the medical students of the Seth G. S. Medical College and some of them showed their interest by asking questions.

The Scientific Sessions was very well attended and a number of papers were read.

Mr. Captain showed how the prevention of accidents was of great benefit to the workers and to the employers. Mrs. K. Choudhury discussed the psychology of industrial accidents of textile workers in Ahmedabad. Mr. Joshi demonstrated some of the cases of industrial accidents who had benefitted by physical therapy in his department at the K. E. M. Hospital. He deplored the attitude of the worker who after an accident tried to get the maximum compensation even at the cost of treatment, and in order to obviate such psychological attitudes, he suggested the granting of the compensation even before the treatment could be started. Mrs. Nimbkar showed the importance of occupational therapy in industrial medicine particularly in regaining finer movements and dexterity after the industrial accident. The delegates paid a visit to the Physical Therapy Department and Occupational Therapy School of the K. E. M. Hospital where they were shown the work carried out and the help which this department can render in industrial medicine. Major Y. K. C. Pandit read a paper on, 'Assessment of Vision of Entrants in Industry' and particularly mentioned the new recommendations of the Ophthalmological Society of India in judging future candidates for jobs. Major Y.K. C. Pandit and Dr. R. L. Mendonca enumerated some of the industries in Bombay where cataract was common and suggested the means of prevention. Another paper on ophthalmology was, 'Foreign Bodies in the Eye,' by Major Tarapore telling of his experience in the subject at the Tata Iron Works, Jamshedpur. Dr. L. B. Banerjee recounted his experience on the treatment and rehabilitation of tuberculous meningitis in the industry with which he is connected. Dr. S. Chakravarty showed how malaria is responsible for the loss of working days of industrial workers and how it can be prevented by suitable antimalarials. Dr. B. Banerjee and Lieut. Col. Najib Khan mentioned different aspects of absenteeism in industry. Absenteeism can be due not only to sickness but also to religious sentiments, as on religious days and also in certain parts due to labourers being part-time farmers. Dr. H. P. Dastur mentioned some of the interesting cases which he had come across in the course of his duties as an industrial physician. A doctor's attitude towards employers and employees in an industry and with his colleagues outside the industry was told in an excellently delivered paper by Dr. Basu. Dr. J. C. Patel and Dr. E. R. De Mello showed that about 76 per cent of the girls working in an industry and 24 per cent of the men had their blood level below the normal average Indian standard. Sixteen per cent of them had signs of nutritional deficiency. They asked the question, whether these workers should be considered as normal Indians because for all practical purposes they carry out the normal factory work, satisfactory to their superiors. Dr. P. S. Mathur told the Conference some of the medical problems connected with the building industry.

A number of scientific films on subjects like industrial dermatosis were shown. The delegates were taken round a number of factories in Bombay which were chosen by the organisers for their interesting features, either from the point of view of industrial hygiene or the medical department.

The social side of the Conference was well organised in the form of a reception to the delegates at a local club and a number of lunches and dinner parties.

The next Conference was invited to Bangalore.

As industrial medicine is a new branch in India, the problems are at the moment mainly of the organisation, accidents, absenteeism and tuberculosis, and these were the problems which were discussed at the Conference, though some outsiders considered other problems like the prevention of industrial cancer, an important subject. As in India there are no industries connected with heavy chemicals, industrial cancer is not a major problem confronting our Industrial Physicians.

BOOK REVIEWS

The Handbook of Medical Management By M. Chatton, S. Margen and H. Brainferd, University Medical Publishers, California, U.S.A. Pp. 475. No illustrations Price. $ 3.

The book has been written by two physicians who have been instructors in medicine in the University of California Medical School, San Francisco and by a third physician who is an Assistant Clinical Professor of Medicine in the same University. The book has been written with a view to help him in his practice or in his internship or house physicianship. This book is also useful to a busy general practitioner as a ready guide for treatment. The book has been written in a style which gives decisive points and sometimes is also dogmatic. However, considering all the aspects of the book, it will be most useful to the majority of medical practitioners. It is priced at 3 $. and can be had from Kothari Book Depct, Parel.

J. C. PATEL.

Atlas of Framboesia, Published by the World Health Organisation: Monograph series. Price: 5/-

The publication fulfills what the title signifies. The clinical descriptions are accurate and are accompanied by excellent photographs illustrating the same. As pointed out by the title, it focuses attention to the protean clinical manifestation of the skin lesions and the authors have avoided the other data about the disease.

The reviewer has a few suggestions and comments to make regarding the author's views about dropping the usual text book classification of the secondary or tertiary yaws. These have been arrived at by observations of the chronological sequences of the manifestations by numerous clinicians. The authors captions on the photographs also bear the same sequences in time duration, *viz.*, that there are cutaneous manifestations which are later in onset than others. Moreover, the same sequence is also seen in syphilis, which is an allied spirochetal disease with more or less identical cutaneous manifestations likely to confuse even a trained clinician. The reviewer would suggest the following classification for the various fræmbesides described by the authors.

Early Fraembesides—Clinical features :—Lesions are early in appearance (within 2 years), comparatively evanescent, non-destructive, usually wide spread, and likely to heal early and spontaneously.

This group would include : (1) Papillomatous fræmbesides (continues to erupt in early stages of the disease, as a rule upto 2 years). (2) Condylomatous fræmbesides which are really the same lesions as above transformed in special sites. (3) Circinate fræmbesides. (4)

Erythematous fræmbesides. (5) Macular, (6) Papular, (7) Desquamative fræmbesides.

Late fraembesides—Clinical features :— Lesions are late in appearance (after 2 years), chronic, tendency to persist without treatment, destructive, likely to heal with scar formation or atrophy, and localised or less wide spread. This group would include : (1) Non-ulcerative hyperkeratotic palmar and plantar fræmbesides, (2) Lupoid, (3) Ulcerative, (or gummatous), (4) Late pigmentary fræmbesides, and (5) Gangosæ.

The above classification helps in clinical approach to cases, understanding the different pathological tissue responses in the two groups, and judging the chronicity of the disease. There may be atypical cases, where the chronology is disturbed, but the pathology is not. They are an exception rather than the rule. A similar situation also prevails in the case of syphilis—the so called "precocious tertiarism." However that does not change the clinical picture, the pathology, or the type of tissue response, on which depend our understanding of the basic disease process underlying protean clinical manifestations. After all, the time is a man made conception and body tissue responses depend the least on it.

S. C. Desai.

CURRENT MEDICAL LITERATURE

MEDICINE

AUREOMYCIN, CHLORAMPHENICOL AND PENICILLIN IN TREATMENT OF BACTERIAL PNEUMONIA, Flippin, H.F., Matteucci, W. V., Schimmel, N.H., and Boger, W.P. : J.A.M.A. 147 : *918-921, 1951.* 6 charts.

Bacterial pneumonia was treated in four different schedules—aureomycin, chloramphenicol, oral penicillin and penicillin by intramuscular injection. Aureomycin was used in an average total dose of 8 Gm., chloramphenicol in an average total dose of 14.2 Gm. The oral penicillin group received 500,000 units initially followed by 250,000 units every 12 hours with a total dose of 3,000,000 units ; the penicillin intramuscular group received an initial dose of 300,000 units procaine penicillin combined with 100,000 units crystalline penicillin followed by 300,000 units procaine penicillin in aqueous solution each day with an average total dose of 3,800,000 units.

The clinical improvement which usually accompanies the reduction of fever in pneumonia points to the cessation of the invasion of toxemia promoting elements, rather than to the antipyretic effect. The critical dropping temperature and its return to normal is considered as an index of the drug's effectiveness in such acute infections. Penicillin, intramuscularly or orally. produces a more sudden drop in temperature than either aureomycin or chloramphenicol. Furthermore, secondary rises in temperature were observed oftener in patients receiving these newer agents. Despite these differences, the end results of all four therapeutic groups were satisfactory. The differences in temperature responses are due to the bactericidal action of penicillin in contrast to the bacteriostatic actions of aureomycin and chloramphenicol. An initial dropping temperature within 24-36 hours is considered an important sign and the treatment of choice in bacterial pneumonia is penicillin. The patients who were treated with oral penicillin responded well in spite of the fact that therapy was discontinuous from the standpoint of failure to maintain demonstrable plasma concentration.

L. K. BANERJI.

TREATMENT OF HUMAN ASCARIASIS WITH HETRAZAN: THE USE OF A SYRUP CONTAINING 1-DIETHYLCARBAMYL-4-METHYL PIPERAZINE DIHYDROGEN CITRATE (HETRAZAN) Loughlin, E. H., Rappaport, I., Joseph, A. A., and Mullin W. G. : The Lancet, 2 : 1197-1200, 1951. 11 references, 3 tables.

The authors have reviewed the literature on the treatment of ascariasis with other drugs like santonin, hexylresorcinol and oil of chenopodium.

They have treated 110 cases of ascariasis in Haiti with three different dosage schedules of hetrazan, given in the form of tablets as well as a syrup of the dihydrogen salt. In the first group of 43 patients, the syrup of hetrazan was given in the dose of 13 mg. per Kg. of body weight, once daily, on each of three successive days. In the second group of 24 patients, a dose of the syrup of hetrazan containing 13 mg. per Kg. of body weight was given on the first day and doses of 20 mg. per Kg. were given, once daily, on the 2nd and 3rd day. In the third group of 37 patients, the syrup of hetrazan containing 13 mg. per Kg. was given, once daily, for 4 successive days. The stools were examined 14 days after completing the treatment, and ascariasis egg counts were made by a technique of S. A. E. X. both before and after treatment. From this, they found that syrup was a better treatment than tablets, as it is useful for any age (the age group of these patients varied between 3-70). Another advantage was the single dosage and they found that a larger single dosage was more effective than a smaller, frequent one. The number of days for which the treatment was required was less. However, as yet with hetrazan there is no one-dose treatment as there is with the oil of chenopodium and hexylresorcinol. There were no toxic symptoms except in one patient, who had symptoms of mild vertigo, loss of appetite and depression. Ninety-one to ninety-four per cent of ascariasis were removed. The authors suggest that it is a useful method for mass treatment in eradication campaigns. The drug had no effect on the egg-counts and hook worms, tape worms and thread worms.

J. C. PATEL.

TREATMENT OF MEGALOBLASTIC ANEMIAS WITH CITROVORUM FACTOR, Davidson, L.S.P., and Girdwood, R. H. : The Lancet, **2** : 1193-1195, 1951. 9 references, 1 table, 1 figure.

The authors have treated six cases of Addisonian pernicious anemia, two cases of megaloblastic anemias of pregnancy and one case of idiopathic steatorrhea by the administration of leucovorin, a growth factor for the streptococcus *Leuconostoc citrovorum*. The chemical formula of this is very similar to that of folinic acid. In all these cases, this factor produced a good clinical and hematological response comparable to vitamin B_{12}. Vitamin B_{12}, in one case of macrocytic anemia of pregnancy, was ineffective where leucovorin was effective. Leucovorin produced a much less striking response in a case of idiopathic steatorrhea, where folic acid produced better results.

J. C. PATEL.

NUTRITIONAL FACTORS IN REPRODUCTIVE FAILURE, Wiesner, B. P., and Yudkin, J. : Nature, **167** : 979-980, 1951. 1 ref. 4 tables.

Evidence has now accumulated from animal experiments that some unidentified nutritional factor or factors contained in the liver are necessary for normal reproductive function. Sub-fertility in women may also be due to similar nutritional factors. Experiments were carried out on a strain of albino rats of Wistar strain. The control and experimental groups were kept on a stock diet on which reproductive activity was known to be good. The composition of the experimental diet is given in the text and it has been known that on such a diet reproduction is at a low level. The diets were employed from weaning for about 23 days and the control males and females employed for mating, were fed on a stock diet. The liver used for supplementing the diet was from raw beef, dried beef and from the cod after the fat was extracted. The rates were paired when 15 weeks old.

The results of this experiment show that there is something in the liver which supplements the purified diet in reproduction even though the experimental diet supported growth and resulted in puberty at the usual age ; animals fed on purified diet took longer to produce litters than those on stock diet. There were smaller litters on the purified diet and the survival of pups was also less. In some cases, all died within 3 days.

The authors are of the opinion that liver contains a nutritional factor or factors necessary for reproduction and not identical with any of the better known factors. They called this factor 'reproductive factor R'. They feel that the vitamin B_{12} content of the liver may account for part but not all its R-activity.

J. C. PATEL.

EFFECT OF VITAMIN B_{12} ON THE SYNTHESIS OF PROTEIN AND NUCLEIC ACIDS IN THE LIVER, Sahasrabudee, M. R., Lakshminarayan Rao, M. V. : Nature, 168 ; 605-606, 1951.

Albino rats were kept on a diet free from vitamin B_{12} for four weeks to deplete as much of their tissue reserves of the vitamin as possible. Intestinal biosynthesis of the vitamin was prevented by oral sulpha in the diet. The animals were kept fasting for a period of 48 hours and re-fed for four days. During the re-feeding period, one group was kept as a control and another parallel group received daily 3 µg. of vitamin B_{12} intraperitoneally. The livers were excised from these animals and studied for protein and nucleic acid synthesis. It was found that there was a greater concentration of liver proteins in those animals receiving vitamin B_{12} and that occurred probably by enhancing amino-acid utilization. There was also an increase in the total nucleic acid content of the liver which was much more than could be explained by an increase in the protein content. It is suggested that this was the first experimental proof that Vitamin B_{12} helps in mammalian nucleic acid and protein metabolism.

J. C. PATEL.

SURGERY

PRINCIPLES OF GENERAL ANESTHESIA IN CHILDHOOD, WESTHEAD, P. : The Practitioner 167 : 514-520, 1951.

The author stresses the need for accustoming the child to the hospital surroundings before operation and the importance of a careful general examination of the child by the anesthetist to exclude any infectious disease especially the common cold.

Premedication should aim at having the child actually asleep so that it should be possible to induce anesthesia without waking him. Nembutal and seconal are commonly used by the oral route and are reliable and safe. By the rectal route. paraldehyde and avertin have been in common use but sodium pentothal is more useful. In all these cases a careful watch must be kept from the moment of administration, to avoid respiratory obstruction. Morphine, omnopon and pethidine may be used in bigger children when pentothal is used intravenously as the inducing agent and are perfectly safe provided the dose is carefully calculated. Atropine must be given to reduce secretions but it should be avoided in the newborn as there is a risk of hyperthermia and convulsions.

Ether is the most common and by far the safest anesthetic agent for children, either by the open drop method or the semi-closed method using a Boyle's or similar machine. Ethyl chloride is very useful as an inducing agent. If with an overdose the child stops breathing artificial respiration must be instituted without delay and continued till normal respiration is once again established. Vinesthine can be used for induction and very short operations but it is unwise to use it for long because of the risk of liver damage. Nitrous oxide is useful for induction and short operations but as children do not tolerate any degree of anoxia, at least 20 per cent oxygen must be used when nitrous oxide is the sole agent.

Trilene, chloroform and cyclopropane are essentially special purpose anesthetics, the two being non-explosive cannot be entirely dispensed with. The main danger of chloroform is in the induction stage where sudden death from ventricular fibrillation can occur even in the healthy child. Trilene is seldom used except as an adjunct to take the place temporarily of an explosive agent. Cyclopropane is used in thoracic surgery but requires a special apparatus and a specialist anesthetist.

SPECIAL TECHNIQUE

Operations for hare lip are usually undertaken at three to six months and the child is best anesthetised with ethyl chloride and ether till at least the second plane of the third stage for intubation. Magill's armoured tubes or Denis Browne's double walled tube are best to prevent compression in the mouth and a loose expiratory valve must be used. The tube must not pass more than an inch into the trachea lest it enter a bronchus and lead to collapse of one lung. Liquid paraffin must not be used to soak the mouth pack as it may set up a lipoid pneumonia. The child must be kept in a very light plane of anesthesia throughout. It is necessary to put on a tongue clip or better still a tongue stitch to help the nursing staff control the airway immediately after the operation. The child is returned in the tonsil position with the head lower than the chest.

For cleft palate operations the child is usually eighteen months to two years old and the same principles apply. Occasionally the surgeon prefers a nasal tube.

Tonsillectomy never necessitates intubation in childhood. The Boyle-Davis gag is used and ethyl chloride and ether can attain adequate depth. Chloroform is not a good agent as the depth needed is too great for safety. In cases of bleeding from the tonsillar bed after tonsillectomy, it is necessary to find out how prolonged and how severe the bleeding has been.

For intestinal obstruction a Ryles tube must be passed to empty the stomach preoperatively and a half normal saline infusion be set up intravenously. No premedication is necessary and atropine may cause serious hyperthermia postoperatively. Intubation is essential in all cases to avoid coughing and spasm in the light plane of anesthesia that is necessary in these cases and to prevent the aspiration of regurgitated stomach contents. Most pediatric surgeons prefer the inconvenience of occasional straining to the addition shock of a deeper plane of anesthesia. For Ramstedt's operation, if general aesthesia is preferred it is never necessary to pass an intratracheal tube. The stomach is emptied beforehand and the baby anesthetised either with ether and oxygen on an open mask, or nitrous oxide, ether and oxygen from an infant size face piece of a Boyle's machine. A much quicker and smoother induction is obtained with a Cope's inhaler and cyclopropane.

EUSTACE J. DE SOUZA.

SKIN GRAFTING FOR THE GENERAL PRACTITIONER, BARKER, D. E. : J.A.M. A. 146 : 1219-1220, 1951.

The author makes an attempt to provide a simple means of skin grafting that can be easily used by the general practitioner. He believes that any wound can be grafted, though naturally, one is more successful if the wound is free from necrotic tissue and gross pus. The long skin grafting knife is not advisable because of the training necessary to master it while pinch grafts almost double the operating time and disfigure the recipient and donor sites. The author prefers the simple and easily operated suction vacutome which does not require special glue or tapes and does not get out of order. Grafts of a thickness of 0.015 of an inch are ideal and are taken with the machine attached to any standard suction. If the dermatome or glue machine is used, the skin should be cleansed with tincture of benzalkonium chloride or thimerosal and after it has dried the area should be thoroughly wiped with an ether soaked sponge. The glue is applied to both skin and drum and should be allowed to dry for five minutes before the machine is applied to the skin.

Holes should be made in the grafts with a No. 11 knife and they should be sewn in place. Bleeding should be controlled prior to the application of the graft. The grafts should be covered with gauze over which a layer of flat sponges should be laid and over this a few fluffed-up sponges kept in place with an elastic bandage. The sponges should be soaked in either 2 per cent boric solution or normal saline, or the first layer of gauze be soaked in petrolatum.

If there is no odour or if there is no rise in temperature above 100°F. the dressings need not be changed for five days.

EUSTACE J. DE SOUZA.

THE MANAGEMENT OF ULCERATIVE COLITIS, Corbett, R. S. : Clinical Journal **80** : 288-294, 1951. 7 figures.

The clinical picture varies considerably and is subject to remissions and complications. Persistent diarrhea, abdominal distress and the passage of blood and mucus lead to a diagnosis of proctitis and possible colitis and it is essential to carry out investigations of the stools to exclude any specific form of infection. An increasing degree of anemia and dehydration become established. The stools become offensive and contain pus. No causative organism has yet been isolated but a toxin vitamin deficiency or irritation within or without the bowel are important factors. The emotional state is very important and the psychosomatic nature of the disease is now well established. The diagnosis requires three important investigations for confirmation. (1)Bacterial examination of the stools to exclude specific forms of colitis. (2) Sigmoidoscopy reveals the characteristic changes in the rectum and lower colon. (3) A barium enema gives very important information.

The treatment, in all cases that are not fulminating, is medical at first—bed rest, high protein diet, starch opium enemata and correction of electrolyte balance. Drugs consist of succinyl sulphathiazole retention enemata, chloromycetin helps to reduce secondary infection and vitamins are essential. Among surgical measures, ileostomy is the treatment of choice though unfortunately it often has to be a permanent one. Colectomy is indicated when the rectal discharge is severe and may keep the patient in bed or where complications are present.

EUSTACE J. DE SOUZA.

A TECHNIQUE FOR TRACHEO-BRONCHIAL TOILET IN THE CONSCIOUS PATIENT, Zück. D. : Anaesthesia, 6 : 226-230, 1951. 3 references, 1 figure.

The author stresses the need for a careful consideration of this problem if pulmonary complications like bronchopneumonia and lung abscess are to be avoided after a serious illness or an operation.

The indications are discussed, special reference being made to its use where the patient is unable to cough freely or where good nursing and carbon dioxide inhalations are not available. Difficulties, like the intubation itself or an active cough reflex are not to be forgotten, as also the inadequacy of laryngeal spraying and the toxicity of the local anesthetics.

The anatomy of the region is described with special reference to the technique used by the author of a superior laryngeal block.

Technique: with a pre-medication of 50 mg. of pethidine, and the patient sitting or lying with the head extended, the nerve is blocked at its point of division slightly below and anterior to the greater cornu of the hyoid, with 2-3 cc. of 2 per cent procaine. Intubation is easier in the sitting position after spraying the clearer nostril with 0.5 cc. of cocaine. A Magill's endotracheal catheter is passed after lubricating it with a water-soluble jelly, and a sterile suction catheter is passed through it.

The smaller catheter is manipulated into the bronchi and any cough that may be stimulated, only helps in the evacuation of the bronchial tree.

EUSTACE J. DE SOUZA.

RESULTS OF SURGERY FOR BRONCHIECTASIS, Chesterman, J. T. : B. J. S. 39 : 263-271, 1951. 7 figures, 15 tables.

The author assesses the results of lobectomy and segmental resection of 114 consecutive resections over a four year period for primary bronchiectasis, on 106 patients. There were 2 operative deaths and 5 later deaths.

Pre-operative routine consisted of physiotherapy to establish normal chest wall function, reduction and sterilization of sputum, removal of iodised oil from the lungs and the reduction of nasal sepsis.

Operative technique: In children the two tourniquet method can be done in half an hour unless glands are present. The dissection method is advised unless speed is essential—*i. e.*, in small children, bad risks and wet cases.

Post-operative routine : A single intercostal drain is used if lung tissue has been cut across, when oozing is present and with a depleted staff. The patient is allowed out of bed and breathing exercises are started in 48 hours.

Morbidity is due to (1) failure of expansion, (2) spread of bronchiectasis, (3) collapse and pneumonitis on the contralateral side and (4) morbidity congenital abnormalities found at operation.

The cough persists in some cases unassociated with sputum and is believed to be the result of over-canalization of the reflex. Nasal sepsis improved astonishingly in all cases. The author feels that operative mortality is due to almost entirely avoidable errors of judgment. Later mortality depends on bilateral and diffuse cases operated upon. Post-operative lack of expansion centres around (1) tracheo-bronchitis (2) pleural fluid. (3) bronchopleural fistula and (4) pulmonary edema and infection.

EUSTACE J. DE SOUZA.

THE USE AND LIMITATIONS OF HEARING AIDS. Ormerod. F. C. : The Practitioner 167 : 504-509, 1951. 6 references.

The history of devices to help the deaf patient is traced from the simplest cupping of the hands to the modern electrically powered aids with their great power of magnification and the ability to selectively increase certain sounds. However, the limitations of the instruments themselves and the types of deafness that can be helped is stressed. The aid that has been specially considered is the 'Medresco' as has been recommended by the Medical Research Council and distributed by the National Health Service.

The object of a hearing aid is usually to enable the subject to hear the conversation of the individual with whom he or she lives which is otherwise difficult or impossible. Others cannot hear well in theatres or in church while others who only hear loud conversation find listening to the telephone very difficult. These represent Grades II, I and III according to the Beasley classification and a loss of hearing from 34-47 decibels in Grade II, 18-33 decibels for Grade I and more than 47 decibels for Grade III as measured on the speech audiometer. Testing for the hearing capacity, after an otologist has ascertained the cause of deafness and whether it can be treated or not, is done by means of tuning forks, conversational voice, pure tone audiometry and speech audiometry, if available.

EUSTACE J. DE SOUZA.

DERMATOLOGY

ANTIQUITY OF SYPHILIS WITH SOME OBSERVATIONS ON ITS TREATMENT THROUGH THE AGES, Cole, H. N. : Arch of Dermat. and Syph. 64 : 12-22, 1951. 55 references.

In this rather long and comprehensive article the author tries to make a strong case against the Columbian or the American origin of syphilis. There are two schools of thought for this proposition. Among the notable authors who believed in the Columbian or American origin of syphilis were Prof. Iwan Bloch of Germany, William Allen Pusey and Sir William Osler of America. "Professor Bloch thinks all available statements and facts point to the last decade of the fifteenth century, particularly the years 1493 to 1500, as the time syphilis first appeared in the Old World. He thinks it was brought to Europe by Columbus' sailors. Bloch argues that the literature of the Old World before 1495 gives no description of the syphilis syndrome. He says Virchow has repeatedly declared that there are no pre-Columbian bones with syphilitic changes".

The author refers to works of many other authors who support the theory of the Columbian origin of syphilis. Regarding the other side the author poses a question : "Was this a condition that had come down through history along with the many other plagues that have affected the human race, or is it actually true that syphilis was brought to the civilised world by Columbus and his sailors when they returned from Hispaniola?" The German medical historian Sudhoff has contanstly fought the idea that syphilis was transported from America to Europe. Prov. J. K. Proksch defends this stand firmly when he says, "There is no question but that syphilis was present in antiquity even though it was not recognised by the physicians" and, "Kensler who spent more than 20 years on the study of the sources of the history of syphilis and on related external diseases, concludes that syphilis, under the form of herpes of the Greeks and fornica of the Arabians, had existed since the memory of man throughout the entire Dark Ages." The author goes on to cite and quote extensively from the various protagonists of either thesis. Columbus did not reach the New World in his ships the Pinta and the Nina until March 15th, 1493. He quotes profusely a host of authors to prove that the disease existed in Europe and other countries long before this date. To use his own words, "In our opinion these reports and extracts go far in showing that long before the end of the fifteenth century there was a venereal disease found throughout the Far East, the Egyptian, Grecian and Roman Empires and Europe in general which was variously called leprosy, leprosy, spuria, aluhumata, sarna, maluum mortuum, saphati, usaphati, wilde Wartgen, mal Frangose, grande verole, gore, elephantiasis, bubas, pudendagra, mal de Naples, *etc., etc.* Holcomb gives the number of different names as around 600. And in 1530 Fracastarius wrote his celebrated poem "Syphilis, sine morbus gallicus". The name syphilis was that of shepherd sick of a disease, non-venereal in type, which had been inflicted on him by a sun god whom he had cursed for killing his sheep, who first used guaiacum, a remedy revealed by a goddess. Sir William Osler says this is the best known medical poem ever written."

While throwing himself heart and soul in the orgy of literature for and against the Columbian origin of syphilis, the author incidentally makes passing references to therapeutic measures adopted for this disease recognised under different names in different countries. Mercury headed the list which included guaiacum, cinchona, sarsaparilla, and sassafars. It is interesting to note that even during those days the present-day vices of hording, monopoly and blackmarketing for a drug in demand were rampant!

Finally the author, after thoroughly reviewing the available literature, puts a poser, "Did syphilis originate in the Americas or was it already prevalent in Europe before the discovery of the New World?" and sums up the reply as follows. "It is believed, that enough authorities have been cited to show that syphilis under various names was well-recognised and treated with mercury in various forms long before the discovery of America. On the other hand, if we are to accept Williams' studies on bones and Ringham's investigations in Peru, there is a possibility that syphilis was also prevalent in the Americans before Columbus touched our shores." The author concludes the article with a doubt whether this debatable problem will ever be solved to the satisfaction of all.

T. K. MEHTA.

CASE OF PEMPHIGUS TREATED WITH ACTH. Rubin, A.: Arch. of Derma. and Syph. 64 : 196-197, 1951.

On reviewing the literature, the author found that there were no reports of cases treated and 'cured' with ACTH. He therefore reports a case successfully treated with ACTH.

The patient was first seen by the author in June 1950. He was 65 years of age and was diagnosed as suffering from "occupational dermatitis". He was treated with aureomycin and appropriate local applications with partial improvement. In July a tentative diagnosis of pemphigus was made as new bullae continued to appear on the ankles, legs, thighs, arms, forearms and abdomen. Itching was annoying on the back. The Nikolsky's sign was present. Two Pels-Macht tests were made and revealed an index of 48, *i. e.*, the test was positive for pemphigus. There were 17 per cent eosinophils in a blood smear differential count which returned to normal. Again the treatment consisted of aureomycin and penicillin injections and local compresses with diminution in the number of bullae to be followed by recurrence. On August 29 (1950) ACTH injections were started in doses of 10 mg. every 6 hours. After 2 days, most of the bullae disappeared, the throat cleared completely and the patient felt very well. Injections were given for 6 days and then being free from all eruptions, the patient left the hospital. Even then the patient continued to take 3 daily injections of ACTH till September 8th, when the number of injections was reduced to 2 in 24 hours. There was slight recurrence during the period of treatment. The injections were discontinued on September 27th. On examination, the patient was completely free from eruptions except for the residual pigmentation and a few bullae here and there. Since then he was free from all lesions till May 3, 1951, There were no side effects of the drug.

It was observed that compared to the other usual therapy, ACTH produced very definite improvement and maintained the remission for a long time.

T. K. MEHTA.

TREATMENT OF CUTANEOUS TUBERCULOSIS WITH LOCAL INJECTIONS OF STREPTOMYCIN, FOSTER, P. D.: Arch. of Derm. and Syph. 63 : 597-605 1951. 4 Photographs.

The treatment of skin tuberculosis has always been a problem as cure is rare, inspite of the various measures available. However, the author has found an apparent solution of the problem by the local infusion of streptomycin, intracaine (beta-diethylaminoethyl para-ethody benzoate) hydrochloride and epinephrine into tuberculous lesions and the surrounding skin area. From his small experience of 3 cases successfully treated with this new method. the author feels that streptomycin thus administered is much more effective and without the side effects of parenteral therapy. The treatment leaves little scar tissue, does not require the maintenance of streptomycin levels in the blood, and can be carried out in one's consulting room.

Discussing the rationale of the new procedure, the author observes that the effective use of streptomycin in the treatment of cutaneous tuberculosis requires (1) that the local concentration be high enough for the drug to act both as a bactericide and as a bacteriostatic agent and (*ii*) that the drug to act on the intracellular as well as extracellular tubercle organisms. The local infusion of streptomycin appears to fulfil both these functions. Besides, the development of resistant strains of tubercle bacilli is prevented by the high local concentration of the drug. This fact is of paramount importance in the treatment of all tuberculous lesions with streptomycin. In other words, for all practical purposes the physician gets only one chance with streptomycin in the treatment of tuberculosis because of the formation of these resistant strains. Streptomycin appears to have both a bactericidal and bacteriostatic action depending to a great extent on the time of contact, the organism involved, the concentration of streptomycin and the size of the area involved.

However, the author is silent on the exact figures regarding the effective concentration and the state of activity of lesion. It may be added that tubercle bacilli do not produce an antagonist to streptomycin. Another factor of importance is the presence of salt in the area. It has been observed that salt has an antagonistic effect on streptomycin. In view of this fact, it would be advisable to keep the blood chlorides low during the infusion period.

Procedure :—1 Gm. of streptomycin is dissolved in 1 cc. of 2 per cent solution of intracaine and epinephrine 1 : 1000, producing a nearly concentrated solution with a bulb of 1.75 cc. and a pH of 4.3. Intracaine mitigates pain and thus a concentrated solution can be infused into a diseased area without any untoward effect. Epinephrine prevents the rapid excretion of streptomycin in the urine and thus helps to maintain a high local concentration. Besides, it lessens the irritating and hemorrhagic properties of streptomycin. The method of administration was by an intradermal infusion with blanching of the epidermis, but without the production of a bleb. To obviate pain, one should inject slowly and with little pressure applied to the syringe. A slight burning sensation, due to low pH of the solution, may be felt at the first injection. The dosage of streptomycin varies with the size of the lesion and the area involved. The author recommends arbitrarily 1 Gm. of streptomycin daily for 20 days. In his cases injections were given daily except where the induration and hemorrhagic bullae precluded further injections until these complications subsided. If the entire lesion cannot be covered in a few injections, it is advisable to cover as large an area as possible and treat the rest the next day from where it was discontinued.

Reports of 3 cases treated in the above manner are included in the text. Two were of lupus vulgaris and one was that of lupus verrucosus. Tubercle bacilli were recovered on culture and on guinea-pig inoculation Tuberculin and patch tests were positive. A roentgenogram of the chest was negative in each case. Lesions cleared up in all patients at the end of treatment without any side effects. In conclusion, the author observes.. "The enthusiasm of initial success should not blind us to the potentialities for even well arrested tuberculosis to relapse. It is well known that tuberculosis which is clinically healed may be undergoing a latent period of inactivity. We should recognise that bacilli may persist for years after the disease appears inactive clinically and be on guard against the danger of premature and erroneous conclusions concerning the lasting effects of streptomycin infusion therapy".

T. K. MEHTA.

SOLITARY MOLLUSCUM CONTAGIOSUM IN ADULTS, Tobias, N. : Arch. of Derm. and Syph. 64 : 208-209, 1951.

Besides the usual typical lesions, pearly semiglobular and umbilicated, molluscum contagiosum may produce atypical lesions, *e.g.*, (*i*) the papular or acuminate, (*ii*) the pedunculated, (*iii*) the corneous and (*iv*) the giant type. To this group of a typical lesions, the author adds the senile solitary type, which has not received sufficient attention in literature. He came across two such cases, one in a woman aged 46 years and the other in a 62 years old man. In the woman there was a solitary semi-translucent pseudopapule, 3 mm. in diameter, just below the right eyebrow, present for the last five months. There were a few crusts on the surface but no central dimple. In the old man there was a non-inflammatory pseudocystic lesion, 4 mm. in diameter on right side forehead, present for one year.

In both, there was no previous history of warty or molluscum lesions. The author suggests that there is probably no immunity to molluscum contagiosum. The appearance, localization and chronicity of the lesion in both the above cases suggested the diagnosis of a cystic basal cell carcinoma until biopsy proved the lesions to be those of molluscum contagiosum. These cases emphasize the importance of performing biopsies on all lesions which suggest carcinoma and of withholding treatment until a definite diagnosis is established. The author concludes with a remark that this solitary type of lesion may be due to an attenuated virus or unfavourable soil.

T. K. MEHTA.

USE OF N-ETHYL-O-CROTONOTOLUIDIDE FOR THE RELIEF OF PRURITUS, Johnson, S. A. M., Bringe, W. J. : Arch. of Dermat. and Syph., 63 : 768-769.

N-ethyl-o-crotonotoluidide was originally introduced as a newly synthesized scabicide in 1946. Later in 1949 its value as an antipruritic was established by Couperus. Impressed by the results obtained by the latter, the authors went on to treat their 121 cases of various dermatoses characterized by pruritis. The series included such diverse conditions as neurodermatitis, lichen planus, psoriasis, pruritus ani, vulvi, or scroti, etc., The drug was used in a vanishing cream base.

As for the results, excellent to moderate relief was observed in 74.3 per cent of the group ; 4 per cent exhibiting reactions. The majority of patients were grateful for this remedy, for though it did not cure the ailment, it controlled pruritus better than did any other preparation. Further, it was desirable because of its lack of odor, lack of staining, and non-aggravation of any co-existing pyodermas. Use of the preparation for over a year did not decrease its usefulness as an antipruritic agent or cause local reaction.

T. K. MEHTA.

THE TREATMENT OF WARTS WITH X-RAYS, Hellier, F. F. : Brit. J. of Derm. 63: 193-194, 1951. 1 graph.

In order to find out the element of psychological improvement in warts the author undertook the present study. Seventy-four patients suffering from warts on both hands were treated with fractional doses of X-rays (three doses of 150 r, unfiltered, at 70 Kv. at four weekly intervals). Each hand was placed under the X-ray tube but only the right hand was treated with actual X-ray dose. The following results were obtained :

Total no. of patients.	No. clearing on exposed hand only.	No. clearing on both hands.	No response.
24	2 +1 partial improvement	27	44

From these results it is obvious that the majority of the improved patients benefitted by suggestion, which is well-known to cure warts in some cases. There might be a slight direct action on the warts as seen in these figures. The author has pointed out the increased incidence of warts in recent times after the war.

T. K. MEHTA.

MELANIN PIGMENTATION AND HEPATIC DISEASE, Whitlock, F. A. : Arch. of Derm. and Syph. 64 : 23-30, 1951.

Diseases of the liver quite often produce skin changes which include such phenomena as the sudden appearance of spider nevi, palmar erythema and gynecomastia.

It is claimed that these changes are produced by the local action of circulating estrogens which the diseased liver is unable to inactivate. A relative increase of blood estrogens can also bring about these cutaneous manifestations. The author of this article came across four cases of liver disease associated with more or less generalised melanin pigmentation. There are no previous records of this skin change associated with hepatic disease and hence he reports in detail four cases of cirrhosis of the liver complicated by generalised pigmentation of the skin only, with no simultaneous pigmentation of the mucous membranes of the mouth.

In order to understand this pigmentary phenomenon associated with liver disease, the author describes another rare melanin pigmentary skin disease, *viz.*, acanthosis nigricans which in 50 per cent of cases is associated with intra-abdominal cancer chiefly that of the stomach and liver. The skin condition itself is benign whether associated with cancer elsewhere or not and it seems to be a a nevoid lesion which is made manifest by some unknown mechanism. To explain both these pigmentary phenomena, the author first briefly summarises the physiology of melanin pigmentation. There is evidence for the presence in the skin of a specific oxidase or series of oxidases which act on tyrosine or dihydroxyphenylalanine to form melanin. It is probable that these oxidases are held in check by certain reducing substances, notably sulfhydryls and ascorbic acid. Before the oxidases can function, it is necessary that a stimulus should be applied which will inactivate these reducing chemicals. There is evidence that many varying stimuli can perform this function. Flesch notes that the reducing substances in the skin, *viz.*, sulfhydryls, glutathione and ascorbic acid are diminished by ultraviolet irradiation as they are all changed to an oxidized form. It is also possible that the circulating estrogen is one of the agents whereby these inhibiting substances themselves are neutralized. This is merely an hypothesis in spite of the clinical evidence that estrogen can lead to melanin pigmentation under certain circumstances. To explain the mechanism of pigmentation in hepatic disease and acanthosis nigricans, the following hypothesis is postulated by the author ; in cases of severe liver damage or relative insufficiency there is a failure of the estrogen-detoxicating mechanism. The free circulating estrogen possibly acts on the skin sulfhydryls and so releases the melanin forming oxidases. The author discusses in detail points in favour of and against this hypothesis. The vitamin B group helps the liver in its estrogen detoxicating function. "Benign" acanthosis nigricans and gynecomastia appearing at puberty are examples of relative insufficiency of the liver to deal with the increased content of blood estrogen at puberty. In order to explain the discrepancy between the incidence of hepatic carcinoma and cirrhosis which are common, and the incidence of associated acanthosis nigricans and pigmentation, the author puts forth a further hypothesis of specific skin sensitivity to estrogens in some patients. Objection is raised to this hypothesis in that, not all cases will show a rise in free estrogen in blood and urine. It will be interesting and informative to do a bio-assay of the urinary estrogen.

From the evidence analysed by him, the author comes to the conclusion that the problem of estrogen inactivation in man is by no means settled. It seems probable that the mechanism in a woman of child-bearing age differs from that in men and post-menopausal women. Alternatively, between the menarche and the menopause, the liver is more capable of dealing with large quantities of estrogen or the tissues are less sensitive to its effects. The theory regarding the role of estrogen in the production of melanin pigmentation is founded on the experimental and clinical evidence of estrogen inactivation by the liver. The evidence is by no means conclusive and the author hopes that this paper will stimulate further interest in the problems raised by him.

T. K. MEHTA.

PEDIATRICS

CITROVORUM FACTOR IN LEUCEMIA, Earle, A. M., Reilly, W. A., and Lawson, W. G., Jour. of Ped. 39 : 560-564, 1951.

The authors report the use of the citrovorum factor to suppress the toxic effects of antifolic acid compounds used in the therapy of acute leucemia. Two cases of leucemia are reported. The first, a 5 year old child with lymphatic leucemia was treated with 0.5 to 1 mg. of aminopterin daily ; the second, a 14 month-old baby with myelogenous leucemia was treated with 5 mg. of amethopterin daily. Both patients developed toxic manifestations like ulcers of the palate and oral mucosa, gastrointestinal discomfort and hemorrhage. Citrovorum was started in doses of 10 million units (0.5 cc.) at first, and then 20 million units (1cc.) daily in the first case, and in doses of 10 million units (0.5cc.) and later, 60 million units (2 cc.) in the second case. The ulcers regressed and melena ceased on the fifth day in case 1, and on the fourth day in case 2. Case 1, unfortunately, developed chicken-pox which in a few hours became hemorrhagic and the patient succumbed. Case 2 was sufficiently improved to be discharged, only to succumb later to hemoptysis and hematuria following acute laryngotracheobronchitis. The authors believe that while citrovorum antagonized the thrombocytopenia due to the antifolic drugs, the same results would have been obtained by reducing the dosage of the antifolic acid drugs.

F. A. NAZARETH.

BELIEVE IT OR NOT

Atherosclerosis is not a natural or inevitable concomitant of ageing. It is not just a disease of old age. It is the cause of a high incidence of death and disability among men in the prime of life. It is a pathological process. It is ten times as common in the obese as in the lean in each age group. Even then, the diagnosis of atherosclerosis is presumptive. Severe atherosclerosis is about twice as common in hypertensives as in non-hypertensives of the same age, sex and adiposity.—B.M.J.

FOR PRACTITIONERS

BRONCHIAL ASTHMA TREATED BY BILATERAL RESECTION OF THE VAGUS. A Report of Six Cases, Clarke, C. A. : Lancet, 1 : 438-440, 1951. 7 refs. (Quoted from Abstracts of World Medicine, 10 : 49, 1951.)

Six asthmatic patients, in whom there was no obvious cause for the attacks and in whom medical treatment had failed, were chosen for operation. All branches of the vagus nerve going to the posterior pulmonary plexus were divided ; three weeks separated the operations on the two sides. The result of the operation was disappointing. Two patients had excellent results, one improved only to relapse, and the remainder showed slight improvement only.

D. D. VORA.

THIOURACIL COMPOUNDS IN THE PREVENTION OF PAROXYSMAL CARDIAC ARRHYTHMIA, Ruskin, H. D. : Lancet, 1 : 134-137, 1951. 9 refs. (Quoted from Abstracts of World Medicine, 10 : 55, 1951.)

Methyl and/or propylthiouracil, in a daily dosage of 0.6 Gm. divided in three parts, was given to 7 patients suffering from paroxysmal cardiac arrhythmia. Two patients had apparently normal hearts, 3 had hypertensive heart disease and 2 had rheumatic valvular disease. None showed evidence of thyrotoxicosis. Electrocardiographic proof of the arrythmia was obtained in 6 cases ; 3 patients had supraventricular tachycardia, 2 had auricular flutter with auriculo-ventricular block, and 2 had auricular fibrillation. In 4 the paroxysms were completely prevented, in 2 they became less frequent, and in 1, who was also suffering from valvular heart disease of rheumatic origin with gross cardiac enlargement, there was no response.

Of the 7 patients, 6 had failed to respond to quinidine. The rapidity of the response of some patients suffering from angina pectoris and paroxysmal arrhythmia to treatment with thiouracil compounds, and their relapse when the drug was discontinued, suggested a similar mode of action in both conditions. Possibly the myocardium was the site of action. In the patients responding to treatment, the drug was effective within a week. In 2 patients the combination of quinidine with a thiouracil compound was more effective than either drug alone.

D. D. VORA.

THERAPY OF HYPERTENSION. THE USE OF VERATRUM VIRIDE ALONE AND COMBINED WITH CERTAIN DIHYDROGENATED ALKALOIDS OF ERGOT, Josephs, I. L. : Ann. West. Med. Surg. 4 : 789-794, 1950. 29 refs. (Quoted from Abstracts of World Medicine, 10 : 58, 1951.)

Veratrum viride contains several alkaloids and acts as a vagotonic. Injection into animals causes a slowing of the respiration and of the pulse, and a fall in blood pressure. In man the drug is given by mouth, the dosage being measured in "craw units," one unit being the minimum lethal dose for this small crustacean. To 25 patients with essential hypertension a test dose of 10 units of veratrum viride was given, after which the optimum daily dose was determined. This varied from 20 to 40 units, taken after breakfast. Toxic reactions included pain in the chest and epigastrium and diarrhea. On account of these reactions only 4 of the 25 patients were able to tolerate a large enough dose of the drug to cause a fall in the diastolic pressure of more than 10 mm. Hg. Of the remaining patients, 10 were then given, in addition

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ORIGINAL ARTICLE

LIVER FUNCTION STUDIES IN MALARIA—II †

P. N. Wahi and M. M. Arora*

CHRONIC MALARIA

Thymol Test :—The thymol test (turbidity and flocculation) was positive in 73.4 per cent of cases out of the 60 cases of chronic relapsing malaria studied in this series. The thymol turbidity test was positive in 66.7 per cent of cases with values varying from 4 to 60 units. The following table shows the thymol turbidity in units in 60 cases of chronic relapsing malaria.

TABLE 10.—*Thymol Turbidity in Units in* 60 *Cases of Chronic, Malaria.*

Turbidity in units.	No. of cases.	Percentage of cases.
1—3	20	33.3
4—5	10	16.6
7.5—10	16	26.6
11—20	13	21.6
21.60	1	1.6

In 5 cases, thymol turbidity failed to become positive while the flocculation test was definitely positive. In only one out of the entire series of 60 cases the thymol turbidity was 5 units with the thymol flocculation reading within normal range. In 39 cases (65%) both the turbidity and flocculation were simultaneously positive.

It can be concluded, from the above findings, that the thymol turbidity-and flocculation tests are more or less equally sensitive in detecting hepatic dysfunction in chronic relapsing malaria.

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† Part I was published in the March number of this Journal.

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TABLE 11.—*Thymol Flocculation in 60 Cases of Chronic Malaria.*

Result.	No. of cases.	Percentage of cases.
0	16	26.6
+	9	15
++	14	23.3
+++	16	26.6
++++	5	8.3

Colloidal Gold Test :—The colloidal gold test was found positive in 51 cases (85%) with figures ranging from one + to four +. The following table shows the colloidal gold flocculation in 60 cases of chronic malaria.

TABLE 12.—*Colloidal Gold Flocculation in 60 Cases of Chronic Malaria*

Result.	No. of cases.	Percentage of cases.
0	9	15
+	15	25
++	17	28.3
+++	12	20.0
++++	7	11.7

In 7 cases, where the thymol test (turbidity and flocculation) gave normal values, the colloidal gold flocculation was positive. In one case the thymol test was positive while the colloidal gold flocculation was within the normal range. The colloidal gold test and the thymol test were simultaneously positive in 38 cases (63.3%) out of the 60 cases of chronic malaria studied. In 8 cases (13.3%) both these tests gave values within normal limits.

The colloidal gold test appears to be more sensitive than the thymol test in detecting liver dysfunction in chronic malaria.

Cephalin Cholesterol Flocculation Test :—Cephalin cholesterol flocculation was definitely positive (two + or more) in 78.3 per cent of cases while in 16.7 per cent it was strongly suspicious positive. Thus in 95 per cent of cases it gave evidence of hepatic dysfunction in chronic malaria.

TABLE 13.—*Cephalin Cholesterol Flocculation in 60 Cases of Chronic Malaria.*

Result.	No. of cases. (after 24 hrs.)	Percentage of cases.	No. of cases. (after 48 hrs.)	Percentage of cases.
0	5	8.3	3	5
+	17	21.6	10	16.7
++	12	20	13	21.7
+++	27	45	28	46.6
++++	3	5	6	10.0

Comparing the results of the three flocculation tests, it was observed that the thymol flocculation was positive in 44 cases, colloidal gold flocculation was positive in 51 cases and the cephalin cholesterol flocculation in 57 cases out of the 60 cases studied in this series. Cephalin cholesterol flocculation test was negative in three cases (5%), and in 2 out of these 3 the other flocculation tests were also negative. In 2 cases (3.3%) the cephalin cholesterol flocculation test was the only test positive.

The cephalin cholesterol flocculation test was found to be the most sensitive indicator of hepatic dysfunction, giving the highest percentage of positives as compared to the other flocculation tests.

Bromsulphalein Retention Test :—It was found to be positive in 90 per cent of cases of chronic malaria. In one case (1.7%), out of the 60 studied, this was the only test positive. The following table gives the bromsulphalein retention after 30 minutes of a 5 mg. per Kilogram body weight intravenous injection in 60 cases of chronic malaria.

TABLE 14.—*Bromsulphalein Retention in 60 Cases of Chronic Malaria.*

Percent of dye retention.	No. of cases.	Percentage of cases.
0—0.5	6	10
2.5—5.0	0	0
5.1—10.5	15	25
11—20	12	20
21—30	15	25
31—40	9	15
over 40	3	5

Total Serum Bilirubin Estimation :—It was found raised above 0.6 mg. per 100 c.c. in 19 cases of (13.6%) in this series. The following table gives the distribution of the total serum bilirubin in 60 cases of chronic malaria.

TABLE 15.—*Total Serum Bilirubin in mg. per* 100 *cc. in* 60 *Cases of Chronic Malaria.*

Bilirubin in mg.	No. of cases.	Percentage of cases.
0—0.2	7	11.7
0.3—0.6	34	56.7
0.7—0.9	5	8.3
1.0—1.5	9	15.0
1.6 and over	5	8.3

Urine Urobilinogen Estimation :—It was done in all the 60 cases of chronic malaria studied in this series and was found within normal limits in all except two cases.

Total and Fractional Plasma Proteins :—Twenty cases (50%) out of 40, in whom these tests were done, showed some degree of hypoproteinemia as judged by our normal standards. The following table gives the total and fractional plasma protein values in 40 cases of chronic malaria.

TABLE 16.—*Total and Fractional Plasma Proteins in* 40 *Cases of Chronic Malaria.*

	Value in Gm.	No. of cases.	Percentage of cases.
Total Proteins	4—5	3	7.5
	5.1—5.8	17	42.5
	5.9—7.0	20	50.0
Albumin	1—2	8	20.0
	2.1—3.0	19	47.5
	3.1—3.5	11	28.5
	3.6—4	2	5.0
Globulin	1—2.2	9	22.5
	2.3—3.0	14	35.0
	3.1—4.0	16	40.0
	4.1—5.0	1	2.5

38 cases (95%) showed some degree of hypoalbuminemia as judged from our normal standards.

Associated with hypo-albuminemia, in 31 out of 40 cases (77.5%) a slight to significant increase in the plasma globulin level was observed.

The albumin-globulin ratio was completely reversed in 17 cases (42.5%) out of the 40 cases of chronic malaria studied in this series and all these cases showed marked derangement of hepatic functions as judged by the other liver function tests.

Determinations of total and fractional plasma proteins were valuable indications of the nutritional status of the patient and the extent of hepatic involvement.

Prothrombin Activity and its Response to Vitamin K :—Measurement of prothrombin activity and its response to vitamin K was done in 43

TABLE 17.—*Prothrombin Concentration and its Response to Vitamin K in* 43 *Cases of Chronic Malaria.*

Concentration.	No. of cases.	Percentage of cases.
Initial concentration upto 50%	35	81.3
Initial concentration above 50%	8	18.7
Concentration above 50% after K	22	51.2
Concentration upto 50% after K	21	48.8
Rise of upto 20% above initial .. concentration after Vit. K	28	56.1
Rise above 20% over initial concentration after Vit. K	15	34.9

cases of chronic malaria. In 81.3 per cent of cases the initial concentration was below 50 per cent of the normal. The following table gives the initial concentration of prothrombin and its respone to vitamin K in 43 cases of chronic malaria.

In 65.1 per cent of cases the prothrombin concentration did not rise more than 20 per cent over the initial level after the intramuscular injection of 10 mg. of vitamin K.

The following table gives a comparison of liver function tests in 60 cases of chronic malaria.

TABLE 18.—*Comparison of Liver Function Tests in* 60 *Cases of Chronic Malaria.*

	Fraction.	Percentage positive.
Thymol turbidity	40/60	66.7
Thymol flocculation	44/60	73.4
Coll. gold flocculation	51/60	85
Ceph. cholesterol flocculation	57/60	95
Bromsulphalein retention	54/60	90
Serum bilirubin	19/60	31.6

The numerator represents the number of positive tests and the denominator the total tests done.

The results have been analysed in table 19 which shows the correlation of positive reactions for each test with the positive reactions given by all the other tests. The majority of the positive reactions were matched by other positive tests.

TABLE 19.—*Showing Number and Percentage of Positive Reactions for Each Test as Compared with the Positive Reactions Given by all the Other Tests in* 60 *Cases of Chronic Malaria.*

	I	II	III	IV	V	VI	No other positive.
I. Pos. thymol turb. ..	40	39/96	39/97	39/97	40/100	16/40	0/0
II. Pos. thymol floc. ..	39/88	44	43/97	43/97	44/100	14/31	0/0
III. Pos. coll. gold	39/76	43/84	51	50/98	51/100	15/29	0/0
IV. Pos. cc. floc.	39/68	43/75	50/87	57	51/89	19/33	2/3.3
V. Pos. bromsulph. ..	40/74	44/81	51/94	51/94	54	19/43	1/1.7
VI. Pos. serum bilir. ..	16/84	14/73	15/79	19/100	19/100	19	0/0

The numerator indicates the number and the denominator indicates the percentage of positive reactions of tests as indicated by the number at the head of the column.

The results of all the tests in this group have been summarised in figure 2. This also indicates their relationship to each other. In only one (1.6%), out of the entire series of 60 cases of chronic malaria, did all the tests give negative results. Fifty-nine cases (98.4%) had one or more tests positive. The majority of the cases had five or six tests positive.

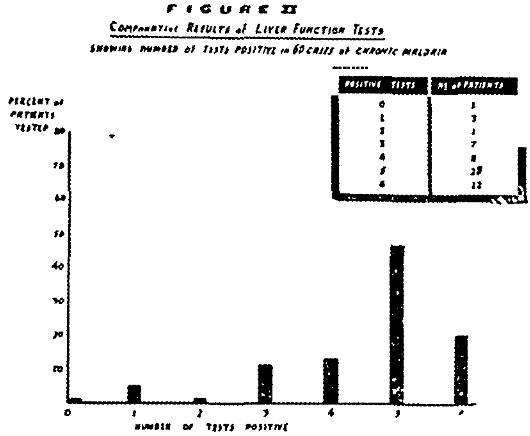

Figure 2.—Showing number of tests positive in 60 cases of chronic relapsing malaria.

The results of various liver function tests were charted on a composite liver function chart (chart 2). The majority of the cases gave a pattern as shown in the chart.

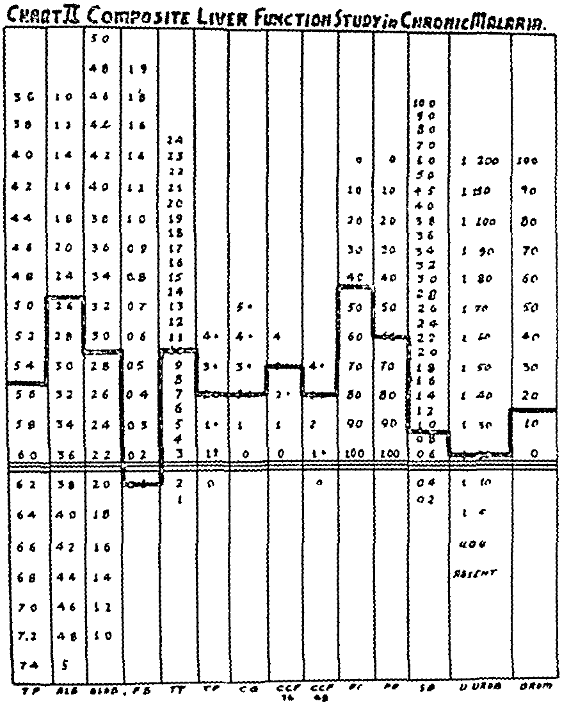

Chart 2.—Composite liver function studies-pattern of response in chronic relapsing malaria.

As in acquired malaria of the acute type, the type of malarial infection and the nature and number of tests showing positive results in chronic malaria showed no relationship. Similar findings were noted with regards to the number of relapses and the duration of the attacks. These, too, had no influence on the extent of liver derangement.

CONCLUSIONS

The investigations that have been reported here, clearly show that in the majority of patients, during acute and chronic phases of acquired malaria, standard liver function tests show some degree of deviation from normal. Ninety per cent of cases of acute malaria showed liver damage as evidenced by the abnormal reading of the function results of one or more tests.

None of the liver function tests used was accurate enough when examined alone as an index of liver dysfunction. Though 60 per cent of cases of acute malaria had only one test positive, the nature of the test varied. Examination of one test alone, such as the case of the levulose tolerance test by Sinton and Hughes[39], and the hippuric acid synthesis by McCorkle[25], in naturally acquired malaria, is therefore not sufficient. On the other hand, the value of serial tests as a measurement of liver function is now accepted.[50], [1], [51], [47]. These results when charted in the composite liver function study chart (chart 1) are more informative.

Chart 1 shows the standard pattern of results obtained in the majority of cases of acute naturally acquired malaria. The deviation from the normal is only slight, and this too is transitory, as was found by the restoration of normal liver function after the termination of the malaria attacks. This observation is in agreement with the findings of Schneider and Shallenberger[37]. Of all the liver function tests, the flocculation tests gave the most positive results in acute malaria, *i.e.*, in 84 per cent of cases. The cephalin cholesterol flocculation test was the most sensitive of the three flocculation tests, as well as of all the individual tests. The next most sensitive individual test was the bromsulphalein retention test.

Results in chronic malaria are more interesting as there appears to be no work definitely describing the effects of long continued low grade or chronic malarial infection. The results of the present investigation definitely suggest that permanent liver damage ultimately results. The nature of the damage is discussed in a separate communication. Of the 60 cases studied, 59 cases (98.4%) had one or more tests positive. The majority of the cases had five or six tests positive. The deviation from the standard normal was also marked, as contrasted to the mild deviation in acute cases. A study of the composite liver function study chart (chart 2) shows the marked deviation from normal as a standard set pattern of deranged liver function in chronic malaria.

Focculation tests were again the most sensitive indicators of damaged liver function. They were found positive in 58 out of 60 cases. Of these, the cephalin cholesterol flocculation gave the most positive results (57 cases). This was closely followed by the bromsulphalein retention test in 54 cases. Serial studies did not reveal much variation though the patients were afebrile in between.

A comparative study of the composite function charts of chronic malaria and liver cirrhosis presents some interesting observations. Deviation from the standard normal is marked in both, more so, in cases of chronic malaria. Structurally, as indicated by the histological studies, the liver is much more damaged in cirrhosis than in malaria. In the latter, the structural changes are confined mostly to reticulo-endothelial proliferation and patchy necrosis, the extensive destruction of liver parenchyma and fibrosis of the diffuse hepatic fibrosis type are never seen. It is therefore to be concluded that liver function deviation depends more on the nature of the structural damage rather than on its degree.

In the present investigation the flocculation tests proved to be the most sensitive. These probably depend principally on changes in the serum gamma globulin. An increase of the gamma globulin occurs in malaria and is probably dependent upon reticulo-endothelial proliferation, which is the most permanent structural change in malaria. This is the observation of other workers [51,3] also. Studies are being made on the correlation of the structural changes in the liver with the nature and degree of hepatic dysfunction, and are likely to produce interesting results.

In this country where malaria is widely prevalent and is endemic in many areas, it was almost impossible, in advanced cases, to distinguish from liver function studies alone, whether the liver damage was due to chronic malaria, or the diffuse hepatic fibrosis was due to malnutrition or chronic epidemic hepatitis. Liver biopsy studies are likely to prove more useful and conclusive.

Both in acute and chronic malaria, the type of malarial infection and the nature and number of tests showing positive results showed no relationship. Similar findings were noted with regard to the number of relapses and the duration of attacks. These, too, had no influence on the extent of liver derangement.

SUMMARY

A study of liver function tests in 110 cases of acquired malaria-50 acute and 60 chronic—is presented.

Liver damage was seen in 90 per cent of cases of acute malaria. This was mild and transitory.

98.4 per cent of cases of chronic malaria had one or more tests

positive, the majority having five or six positive. This damage was more or less of a permanent nature.

It is concluded that the degree of the deviation of the liver function results, from a standard normal, is dependent more on the nature of the structural changes rather than on its extent.

The type of malarial infection and the nature and number of the tests showing positive results had no relationship.

The number of relapses and the duration of the attacks had no influence on the extent of liver derangement.

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ORIGINAL ARTICLE

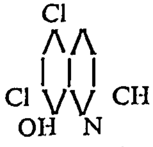
TREATMENT OF CHRONIC INTESTINAL AMEBIASIS WITH A NEW OXYQUINOLINE COMPOUND

H. Wenger *

Among the diseases which are prevalent in the tropics, infection by *Entamoeba histolytica* occupies a very important position. American literature states that the incidence of this infection, in many tropical territories, is higher than 50 per cent. As far as our territory is concerned (Southern Maharashtra) this figure, in our opinion, is certainly not too high.

Acute forms of amebic dysentery are rarely observed in the local population. The chronic forms with a number of undetermined complaints such as irregular stools, temporary loss of appetite, a feeling of fullness, flatulence, lassitude, headache, loss of weight and anemic conditions with symptoms of giddiness are met with much more frequently. As for the differential diagnosis, such cases frequently give rise to difficulties. Although cases of infections with *E. histolytica* rarely represent serious states of illness, the disease, nevertheless, plays a very important role because it affects the general condition seriously and thereby not only lowers the working capacity but also clears the way for other infections on account of the lowered resistance. The fight against this infection is, therefore, of the greatest significance. The elimination of infectious sources, by improving hygienic conditions, would be the most effective method and while this is partly aimed at, it frequently is without success. Very often the necessary supply of water is lacking but in particular it is a lack of education and instruction of the people concerned. The effective treatment of amebic infections, by means of medicaments, began with the introduction of emetine into the range of therapeutic agents. Since then, numerous other medicaments have been added. These are mainly derivatives of oxyquinoline sulphonic acid or arsenic compounds.

We carried out trials of a new oxyquinoline compound about a year ago in the treatment of intestinal amebiasis. This was 5,7-dichlor-8-hydroxyquinaldine which is available in tablets of 0.1Gm. The structural formula of this new hydroxyquinoline derivative is as follows :—



We had occasions to treat a large number of patients with this medicament but can evaluate the results of only a small number, *i. e.*, those

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* Basel Mission Hospital, Gadag, Betgeri, Dharwar District.

TABLE 1.—*Results of 26 Cases Treated With the New Compound.*

No.	Patient.	Stool examination for E. hist.			Treatment with Siosteran.	Subsequent Controls Date and results.
		Date.	Veg. Forms	Cysts.		
1	K. G. 24 years	14.7	—	+	2 tablets t.d.s. for 2 days 2 ,, b.i.d. ,, 2 ,, 1 ,, t.d.s. ,, 2 ,,	1 Control, neg.
2	K. A. 32 years	17.7	—	+	2 ,, b.i.d. ,, 5 ,,	1 Control, neg.
3	A. C. 32 years	25.7	—	+	1 ,, t.d.s. ,, 6 ,,	Stool at the end of 6 days treatment negative in respect of ameba. But there is still diarrhea and leukocytes and erythrocytes in the stool. Picture of a mixed infection with bacillary dysentery. After another 10 tablets all symptoms disappeared. Further observation in hospital for two weeks.
4	G. G. 24 years	8.8	+	—	2 ,, b.i.d. ,, 5 ,,	*Abscess of the liver.* Stool examinations on 15.8, 18.8, and 3.9, negative. On account of the continuing liver symptoms emetine injections and chinifon-enemas were given. Resulted in clinical recovery.
5	N. G. 24 years	18.8	—	+	2 ,, b.i.d. ,, 4 ,,	22.8 neg. 8.9 neg.
6	D. A.	20.8	+	—	2 ,, b.i.d. ,, 4 ,, 2 ,, b.i.d. ,, 2 ,,	(1) 31.8. *E. hist.* pos. (2) then on 5.9 neg. 8.9 neg.
7	G. A. 32 years	18.8	—	+	1 ,, b.i.d. ,, 8 ,,	1 Control, neg.
8	B. N. 10 years	25.7	—	+	1 tablet b.i.d. for 4 days	2 Control, neg. neg.
9	H. A. 60 years	29.8	+	—	2 ,, b.i.d. ,, 5 ,,	2 Control, neg. neg.
10	A. P. E. 26 years	13.9	—	+	2 ,, b.i.d. ,, 4 ,,	1 Control, neg.
11	L. P. 45 years	8.9	—	+	2 ,, b.i.d. ,, 5 ,,	1 Control, neg.

TABLE 1.—*Contd.*

No.	Patient.	Stool examination for E. hist.			Treatment with Siosteran	Subsequent Controls Date and results.
		Date.	Veg.Forms	Cysts.		
12	L. Th. 25 years	13.9	+	—	2 ,, b.i.d. ,, 4 ,,	1 Control, neg.
13	S. B. 42 years	13.9	+	—	2 ,, b.i.d. ,, 4 ,,	2 Control, neg. neg.
14	H. S. 36 years	16.9	+	—	2 ,, b.i.d. ,, 4 ,,	2 Control, neg. neg.
15	S. L. 30 years	17.9	—	+	2 ,, b.i.d. ,, 4 ,,	1 Control, neg.
16	B. J. 28 years	17.9	+	—	2 ,, t.d.s. ,, 3 ,,	2 Control, neg. neg.
17	Sh. A. 40 years	18.10	—	+	1 ,, t.d.s. ,, 3 ,,	3 Control, neg. neg. neg.
18	K. N. 48 years	15.10	+	—	2 ,, b.i.d. ,, 3 ,,	1 Control, neg.
19	S. R. 8 years	24.10	+	—	½ ,, b.i.d. ,, 5 ,,	1 Control, neg.
20	H. J. 11 years	20.10	+	—	½ ,, b.i.d. ,, 5 ,,	1 Control, neg.
21	Th. Y. 22 years	4.11	+	—	2 ,, b.i.d. ,, 5 ,,	1 Control, neg.
22	J. R. 23 years	2.12	+	—	2 ,, b.i.d. ,, 5 ,,	2 Control, neg. neg.
23	N. B. 25 years	11.11	+	—	2 ,, b.i.d. ,, 5 ,,	3 Control, neg. neg. neg.
24	Y. N. 28 years	10.11	+	—	2 ,, t.d.s. ,, 3 ,,	2 Control, neg. neg.
25	R. K. 45 years	25.11	+	—	2 ,, b.i.d. ,, 4 ,,	1 Control, neg.
26	K. G. 29 years	23.12	—	+	2 ,, t.d.s. ,, 4 ,,	3 Control, neg. neg. neg.

cases in which we obtained a clearly positive stool examination before the treatment and with whom at least one miscroscopic examination was carried out after treatment. Very frequently the patients did not come again for a subsequent examination which speaks in favour of their feeling recovered, but this does not signify that a single stool examination after the completion of treatment (even though negative) is not a conclusive proof of cure. However, in the circumstances it is all that we could do.

Despite drawbacks, we feel justified in publishing the results of treatment with the drug. After a critical survey, the number of cases recorded and of interest for this survey is reduced to 26. In all, we were able to satisfy ourselves of the records of 26 cases the summary of which is presented in the table.

E. histolytica either in vegetative forms or cysts, were present in 26 cases before treatment. After the treatment with the intestinal antiseptic, on microscopic examination of the stool, we observed negative findings in all cases, basing these results in 12 cases of only one control, in 10 cases of 2 subsequent controls and in 4 cases of 3 subsequent controls. In one case (No. 6) the first control after the treatment was still positive. After 2 further days of the same treatment, 2 subsequent controls were negative.

In one patient (No. 4), we found symptoms of a fairly severe amebic hepatitis which disappeared only with emetine injections while the stools had become clearly negative after the administration of the intestinal antiseptic.

Dosage :—To adults, 2 tablets twice daily, for 4 to 5 consecutive days were given, *i.e.*, 16 to 20 tablets for one term. Our patients are mostly people with a body weight about 1/3 lower than that of Western Europeans.

CONCLUSIONS

(1) Twenty-six cases of chronic intestinal amebiasis were treated with a new oxyquinoline compound. (2) The results in the treatment of amebic infections of the intestine are satisfactory throughout when compared with the results obtained with other preparations. (3) We never observed any side-effects and had no complaints whatsoever from our patients. (4) The medicament is free from iodine which may be of particular importance for patients who are sensitive against iodine.

ACKNOWLEDGMENT

We take this opportunity of thanking Messrs. J. R. Geigy S. A., Basle, Switzerland for supplying this new oxyquinoline compound V. R. 764—Siosteran, free of charge.

ORIGINAL ARTICLE

RADIOLOGICAL ASPECTS OF BRONCHIECTASIS *

Madan Lal Aggarwal †

During life, radiology offers the only means of a correct diagnosis of bronchiectasis. A diagnosis of bronchiectasis can be made in a high proportion of cases on a plain Roentgenogram depending upon the experience of the radiologist. Such a diagnosis should always be confirmed after bronchography with a contrast medium.

A plain Roentgenogram may show closely packed tiny circles varying from one to three millimetres in diameter giving the appearance of a honeycomb to the part of the lung involved. A lipiodol Roentgenogram shows multiple saccules. A portion of the lung field, usually the lower lung field, may show sharply outlined hairline streaks sweeping across it and running parallel to each other, enclosing columns of air (Fig. 1 and 2). These appearances are seen in cylinderical bronchiectasis and are produced by the thickened walls of the dilated bronchi. Sometimes, ribbon-like shadows are seen traversing the lung field when the dilated bronchi are full of secretions. A combination of parallel streaking and honeycombing may also be seen (Fig.3 and 4).

A Roentgenogram may show multiple cystic shadows with thin walls and a healthy looking lung parenchyma. Their sizes vary from three millimetres upwards. Lipiodol bronchography reveals interesting features. In a large proportion of such cases the cystic appearances are associated with atelectasis and dilatation of the main bronchi. A careful study of the bronchogram reveals, that the so-called cysts are either ballooned out ends of hugely dilated bronchi (Fig. 5) or they are outpouchings from the side walls of bronchi with wide communications with them (Fig. 6). In some cases a cystic dilatation may be seen to involve the whole circumference of a portion of a bronchus. Beyond this dilated portion, the bronchus may be seen to be continued with its normal calibre. It is quite obvious that such cases are not of developmental origin.

Another group of cases shows such cysts in normal sized segments of the lungs with normal calibre of the main bronchi (Fig. 7). Such cases may be of a developmental or of a congenital origin.

It is a good practice always, to study the portion of the lungs covered by the shadow of the heart. An atelectatic lower lobe presents a triangular opacity on the side of the spine. This opacity is only slightly

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* Paper read at the Annual Conference of the Association of Physicians of India, at Amritsar in March, 1951.

† From the Department of Radiology, V. J. Hospital, Amritsar.

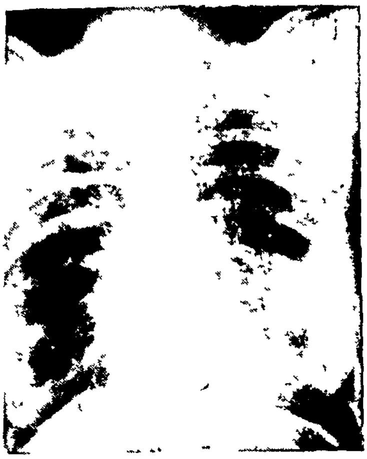


Fig. 1.—Notice sharply outlined hairline streaks sweeping across the lower part of the left lung field, and running parallel to each other enclosing columns of air.

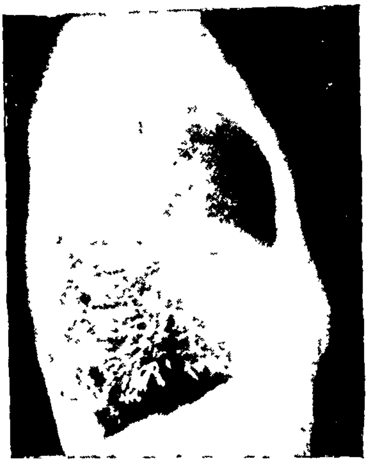
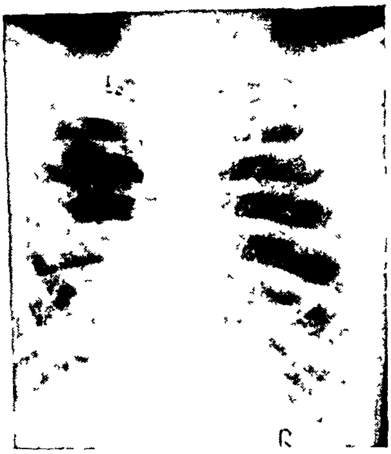
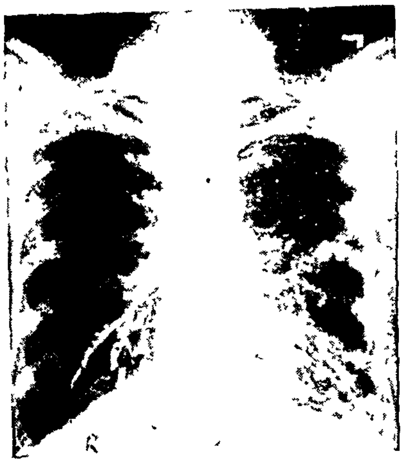


Fig. 2.—Dilated bronchi seen after lipiodol in the case illustrated in Fig. 1.





Figs. 3 *and* 4.—Notice a combination of parallel streaking and honeycombing in the plain skiagram 3 and the cystic and cylinderical bronchiectasis which produced these appearances proved to be present after lipiodol in skiagram

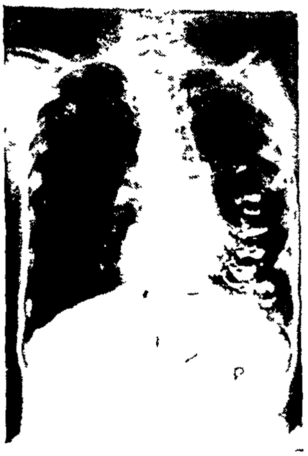


Fig. 5.—Lipiodol bronchography shows that the cystic shadows are in fact ballooned out ends of hugely dilated bronchi.

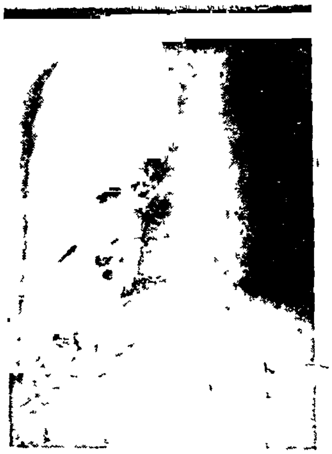
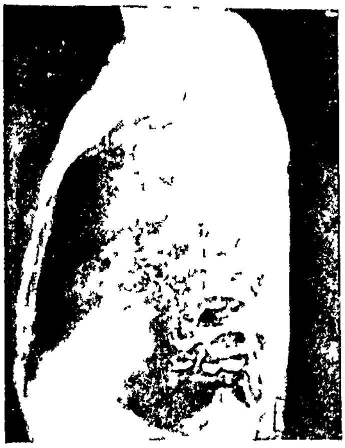


Fig. 6.—Bronchogram of the left lung in the same case shows cystic dilatations of some of the bronchi. Notice that at the arrow mark the dilatation is involving the whole circumference of a portion of a bronchus and that



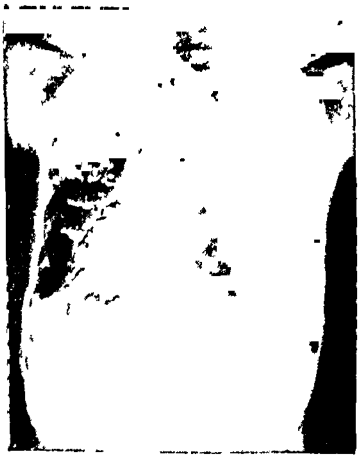
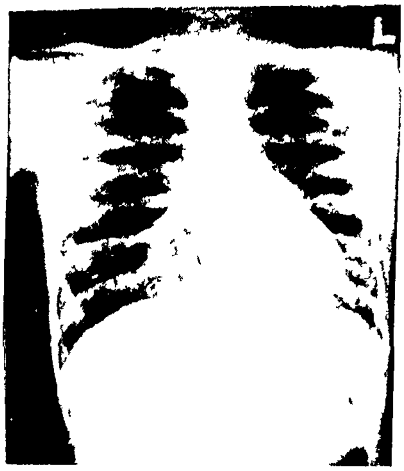


Fig. 7.—Notice that on lipiodol bronchography the cystic shadows in figure 8 are not associated with dilated bronchi and that the size of the involved segment appears to be normal. Such cases may be of congenital origin.



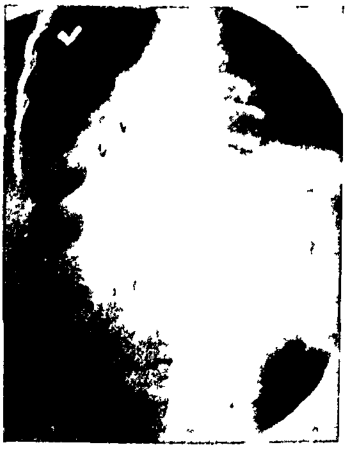
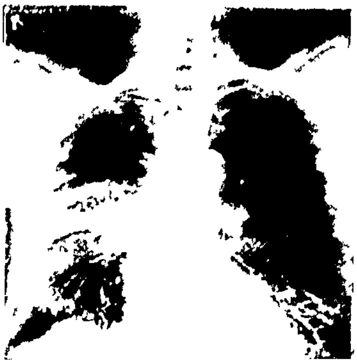


Fig 9.—Notice bronchiectasis in the collapsed lobe and also the involvement of the bronchi of the adjoining lung on the same side and of the bronchi of the opposite lung in bronchiectasis. Also notice that some of the bronchi of the lower lobe of the opposite side are swinging towards the left side which shows collapse of the lower lobe.

Fig. 10.—The heart is shifted to the left. Clinically the case is a case of bronchiectasis. Collapse of the left lower lobe was suspected and an over-exposed film using a Potter- Bucky grid shows the collapse.



denser than the shadow of the heart and can be easily missed, particularly on the left side. Lipiodol bronchography reveals, that such triangular opacities are always associated with well developed bronchiectasis (Fig. 8). Not only are the bronchi of the atelectatic lobe dilated, but the bronchi of the adjoining lobes of the same and even of the opposite lung are also often dilated, presumably, because of the changes in the intrathoracic pressures consequent to the collapse of a large portion of a lung. The dilated bronchi of the neighbouring portion of the opposite lung may be seen to swing across the middle line to the affected side (Fig. 9). These triangular opacities can be beautifully demonstrated in some cases with overexposed films, using a Potter-Bucky diaphragm (Fig. 10).

It appears that atelectasis plays an essential role in the causation of bronchiectasis. Dilated bronchi are almost always huddled together and atelectatic lobes are always associated with bronchiectasis. Whereas atelectasis is always associated with bronchiectasis a fibrosed lung may sometimes show bronchi of normal calibre (Fig. 11). Bronchiectasis is, however, seen quite often in fibrosed lungs (Fig. 12). It appears that the loss of elasticity of the lung in fibrosis facilitates the production of bronchiectasis.

Lipiodol bronchography of all the bronchi of both the lungs should always be done before surgery is undertaken. It helps in the identification of the lobes involved in pulmonary atelectasis and hence in bronchectasis, and it reveals to the surgeon the exact extent of the disease. Extensive bilateral involvement will contraindicate surgery. It makes segmental resections possible. Identification of the dilated bronchi also helps in postural drainage.

ACKNOWLEDGMENT

I have to thank Dr. Y. S. Bawa for doing the bronchographies for me with the technique he has himself developed.

FOR BODY AND MIND

Rest in bed is in itself the cure of many maladies, especially ailments of the fatigue group, minor heart troubles, and nervous disorders. Many patients take to it readily, as a retreat from the turmoil of the hour, but others protest against it and say : "Why should I not dress and lie on the sofa with a rug over me, which is just the same thing?" But it is not the same thing, for there is in rest in bed an abandon and sense of tranquility which the best upholstered sofa cannot afford, and it gives overstrained organs like the heart time to rally and recuperate.

Sir James Crichton-Browne (1840-1938)

HUMBUG

In a large city there were three eminent consultants of world-wide reputation ; one was said to be good physician but no humbug, the second was no physician but a great humbug, the third was a great physician and a great humbug. The first achieved the greatest success, professional, and social, possibly not financial.

Sir William Osler (1849-1919).

ORIGINAL ARTICLE

ANTIMICROBIAL ACTION OF VITAMIN C ON M. TUBERCULOSIS AND SOME OTHER PATHOGENIC ORGANISMS.

M. Sirsi *

That ascorbic acid plays a role in endowing the individual with an increased power of resistance is indicated by studies on guinea pigs receiving injections of diphtheria toxin following graded allowances of ascorbic acid[2],[4]. Animals given ascorbic acid had slightly more circulating antibodies than those deficient in ascorbic acid. That the vitamin is essential for the integrity of certain cells of mesenchymal origin is well known. The collagen of all fibrous tissue is affected, resulting in the irregular formation of fibrous tissue[3]. An increased requirement of vitamin C in man has been reported in infectious diseases and particularly in tuberculosis where the needs are increased a hundred per cent[5].

Despite the vast clinical literature of the various therapeutic indications for vitamin C, and though the vitamin has been reputed to give specific benefit in most known diseases, there is no conclusive evidence that ascorbic acid is of value, except in the relief of symptoms associated with scurvy. The following studies were undertaken to elucidate whether the beneficial results observed after the administration of vitamin C in bacterial infections were merely non-specific in nature or whether the vitamin also exerted a direct bacteriostatic or bactericidal action on these organisms.

I. THE "IN VITRO" EFFECT OF VITAMIN C ON M. TUBERCULOSIS.

The effect of the vitamin on *M. tuberculosis* was studied in the modified Proskaeur and Beck media. Two strains of *M. tuberculosis* were used, one the H_{37} Rv (obtained from N.C.T.C. England) and another strain D_{13}, a virulent strain isolated locally from a case of pulmonary tuberculosis[6]. The surface culture technique[7] was the one used and the results were read at the end of each week till the end of 28 days. Subcultures were also taken at the end of each week. Table 1 records the results obtained.

A bactericidal effect was noticed in concentrations of 100 μg. / cc., and above, from the end of first week and no growth was seen even at the end of three months. 10 μ g. / cc. dilution inhibited the growth

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* Pharmacology Laboratories (Biochemistry Dept.), Indian Institute of Sciences, Bangalore.

TABLE 1.—*In Vitro Tuberculostatic Action of Vit. C at the end of 4 Weeks.*

Strain	Concentration μ g/cc.						
	1000	100	50	25	10	1	0
H37 Rv	—	—	±	±	±	++	++
D13	—	—	±	±	+	++	+—

— No growth ± faint growth + and ++ various grades of growth.

for a period of three weeks after which time the organisms were noticed to start multiplying.

To study the effect of variation of the inocula on the bacteriostatic action, the experiment was conducted using approximately twice the amount of the inocula as that in the first series. Table 2 gives the results obtained.

TABLE 2.—*Tuberculostatic Action of Vit. C on a Heavier Inocula of M. tuberculosis.*

Strain	Concentration μ g/cc.				
	1000	100	10	I	0
H37 Rv ..	—	+	++	++	++
D13	—	+	++	++	++

It will be noticed that the tuberculostatic action of vitamin C is very much diminished in the presence of the large inocula but it is still found to be bactericidal at 1000 μ g. / cc. dilution.

II. "IN VITRO" ACTIVITY OF VITAMIN C ON SOME PATHOGENIC BACTERIA

Ascorbic acid was dissolved in suitable media so as to give an initial concentration of 1/100 and sterilized by Seitz filtration. The standard serial dilution method was adopted and the results were read at the end of 24 hours using the Klett-Summerson photo-electric colorimeter for measuring the turbidity. Table 3 summarises the results obtained.

TABLE 3.—"*In Vitro*" *Bacteriostatic Action of Vitamin C on Some Pathogenic Bacteria.*

Organisms	Concentration.			
—	1/100	1/250	1/500	0
Staphylococcus aureus	—	—	+	+
Streptococcus pyogenes	—	±	+	+
Bacterium coli	—	+	+	+
E. typhosum	—	±	+	+

— bactericidal ± bacteriostatic + no inhibition

Subcultures were taken from the different dilutions and Table 1 also indicates the bacteriostatic or bactericidal effect.

It is seen that in a 1 per cent dilution, vitamin C is bactericidal to all the above organisms, whilst its inhibitory effect is completely lost even at 1/500.

A comparison of the action of vitamin C and *M. tuberculosis* and other organisms, clearly indicates that vitamin C in concentrations which could be obtained in the body after vitamin C therapy can exhibit a direct bacteriostatic action on *M. tuberculosis* sometimes being even bactericidal in nature, while no such result can be obtained against other pathogenic bacteria.

It is probable that besides beneficial non-specific reactions, vitamin C has a direct role in modifying the course of infection in tuberculosis.

SUMMARY

1. Vitamin C is known to endow the individual with increased powers of resistance to infection. Whether the effect was the result of non-specific reactions or the vitamin exerted a specific action on the microbes was the subject of this study.

2. An "*in vitro*" evaluation indicates that vitamin C has tuberculostatic properties against virulent strains of *M. tuberculosis* in fairly high dilutions.

3. An increase in the amount of the inocula reduces the tuberculostatic action of the vitamin.

4. Vitamin C does not inhibit the growth of staphylococci, streptococci, *B. coli* and *E. typhosus* to the same extent as *M. tuberculosis* in comparable dilutions.

5. It is suggested that vitamin C in concentrations that could be obtained after vitamin C therapy in the body, has a direct role in modifying the course of infection in tuberculosis but not in the diseases caused by other organisms mentioned in the above study.

The selective and differential concentrations of vitamin C attained in the various organs of the body after vitamin C therapy, the variations in the course of tubercular infection after vitamin depletion and large doses of vitamin C therapy in experimental animals, are under investigation.

ACKNOWLEDGMENT

My thanks are due to Dr. N. N. De and Dr. K. P. Menon for their valuable suggestions.

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CANCER

"Cancer research has reached a stage at which the following affirmations can be safely made :

> "The exciting causes of cancer are multiple and complex. In fact cancers may now be induced experimentally at will by (*a*) genetic manipulations, *i.e.*, inbreeding, selecting and cross-breeding (*b*) injection or feeding of any of several hundred chemicals, some of which are organ specific (*c*) hormonal imbalances and disturbances (*d*) many of the energy agents (roentgen, gamma, radium and ultraviolet rays) especially in animals that are subjected to interval exposure (*e*) a combination of two or more of the aforementioned factors. It seems unmistakably clear that no single specific agent or condition or any combination of agents or conditions is responsible for the initiation of all types of cancer."
>
> R. R. Spencer, J.A.M.A. 1948, **137**, 1361.

My view might be put in the form of a three-act play :

Act 1. Frontier town. Oppression by foreign thugs, called Carcinogens. Communist rising, which is quelled by regular troops. (Interval of twenty years).

Act 2. Capital city. Decline and fall of the reigning house, the Gonads.

Act 3. Frontier town again. The old grievance resurrected. Communist rising again. Successful spread throughout kingdom. Dissolution, Curtain.

'The Phoenix Cancer' Medical World, Jan. 4, 1952, Pg. 488.

STUDY OF GROSS AND MICROSCOPIC EXAMINATION OF TUMORS.

M. V. Sirsat *

The Tata Memorial Hospital in Bombay, which is a cancer hospital deals with only neoplastic diseases and affords ample opportunities for studying a large number of tumors occurring in various parts of the body. With the experience of the past several years a definite plan of approach in the study of neoplastic material has been worked out, which if followed, leads to success in the diagnosis of tumors. It is the purpose of this paper to outline this plan, in the belief that it is worth doing so in the light of some unfortunate experiences we had while reviewing the slides and material referred to us from the mofussil and from a few large city hospitals. Some of the material has been sent to us in the most unsatisfactory manner and we are convinced that in a large proportion of instances the wrong selection of representative areas of tumor portion, poor fixation and staining has been the cause. It is therefore thought that the methods followed in this laboratory in the study of tumors, which have given us such fruitful results might be of interest to those dealing with tumor material. No originality however is claimed in the methods, for many of these are based on the work of other authors.

At the time of operation for a malignant neoplasm a pathologist will frequently be called upon to determine whether the surgeon's line of incision is or is not beyond the neoplasm. This is very important as the sole object of the operation will be defeated if a portion of a malignant tumor that could have been detected at the time of operation is left behind in the patient. A pathologist may also be required to make a diagnosis by macroscopic examination of the lesion, *in situ*, while the patient is on the operating table and the operation is in progress. It may be necessary for him to make a microscopic examination by rapid methods while the operation is in progress, in order to determine what should be the further procedure of the surgeon. So in the practice of modern surgical pathology, the pathologist, in order to render efficient service to the patient and the surgeon at the time of operation, must have at his command a small laboratory equipped to make frozen sections of fresh tissue for microscopic examination. The proximity to the operation theatre of such a laboratory needs special emphasis as an easy access is a chief requisite. In view of the fact that the decision of the surgeon regarding a conservative or radical operation is largely made on the findings and report of the pathologist on the microscopic examination of the tissues, the pathologist has to be very careful and should at all times, exercise good judgment. Frozen sections should be used as sparingly as possible. Frozen sections, undoubtedly have a great value in tumors of the breast. The results of frozen sections which are done in this hospital only for tumors of the breast have been very gratifying. Here reference may be made to a recently published paper[8] relating to a study of 25 cases at this hospital where it was observed that valuable information has been given to the surgeon in 9 cases ; in 5 other cases where the clinical diagnosis was carcinoma, frozen section has revealed a benign lesion ; and in 4 cases, carcinoma has been disclosed where the clinical diagnosis was a benign tumor. It will be seen from this that 5 cases were saved from undergoing a radical operation. After the publication of this paper over 300 frozen sections have been carried out in breast tumors, all with the most gratifying results. The pathologist is always in a much better position to make the diagnosis if he has all clinical information available before the frozen section is done. It is often also helpful for him to examine the patient before this procedure.

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* Department of Pathology, Tata Memorial Hospital, Parel, Bombay.

GROSS EXAMINATION OF SPECIMENS

After a careful examination with the naked eye, the specimens should be measured, weighed and described carefully. . Such a procedure helps to document the case and will prove valuable for follow up purposes.

The specimen is then subjected to microscopical examination. Specimen blocks, not more than 4 mm. in thickness are cut with a sharp knife. In cutting such blocks, it is absolutely necessary to use selective judgment and the pathologist himself should select representative areas of tumor for sectioning and should never entrust this job to the technicians. The tissue should be carefully inspected, if necessary, with a hand lens, and those areas, which show the most characteristic gross lesions should be chosen for processing and microscopical study. One should never cut blocks from necrotic foci as is so often done in the case of tumors.

FIXING PATHOLOGIC MATERIAL

It is our unfortunate experience that we have often received tissues put in all conceivable fluids used as fixatives. Such 'fixatives' have been Eau de Cologne, methylated spirit, rectified spirit, normal saline and even water. Such fluids must be condemned as fixatives as they only help to bring about an autolysis or destruction of cytological appearance beyond recognition. The tissues must be fixed in an appropriate fixative such as formalin saline, Bouin's or Zenker's fluid. The volume of the fixing fluid should be 20 times more than that of the tissue. All the specimens in this laboratory are fixed in formalin saline. Those that are important, and unusual types of tumor are also fixed in Bouin's and Zenker's fluid.

Formalin Saline :—0.85 per cent aqueous solution of sodium chloride, 90 cc. formalin (40% formaldehyde)—10 cc.

Bouin's Fluid :—Alcohol 80 per cent—150 cc., formalin—60 cc., acetic acid (glacial) 15 cc., picric acid—1 Gm.

Zenker's Fluid :—Potassium bichromate 2.5 Gm., corrosive sublimate 5—8 Gm., distilled water—100 cc., glacial acetic acid—5 cc.

Glacial acetic acid evaporates rapidly and produces changes in the chrome salts in a prepared stock solution. It is therefore found best to use modified Zenker's solution. I. Potassium bichromate—25 Gm. ; Mercuric bichloride (corrosive sublimate)—50 Gm. ; Distilled water—1000 cc. ; II. 40 per cent neutral formalin. These solutions are kept separately. Mix 9 parts of solution I to 1 part of solution II before use.

If tissue is fixed in formalin and simultaneously in Bouin's and Zenker's fluid, one obtains varying strains of histologic pictures. Bouin's solution results in brilliant color effects and contrasts. Zenker's fluid has no rival for giving clear and sharp details. Thus each one of the solutions gives a variation which helps to obtain a clear composite idea of the true morphology of the tissue under examination. If the tissue is to be transmitted to the pathologist by post, the surgeon himself should be responsible for the specimen. The selected specimen should be put in a bottle containing formalin saline and should never be squeezed into it.

STUDY OF OPERATED MATERIAL

The operative specimens should be stuaied according to a definite plan, if one has to obtain fruitful results. Such a study although time consuming has its rewards. It is a great advantage to examine the gross specimen in collaboration with the operating surgeon. This is helpful to the pathologist for a correct orientation of the tumor, and it helps the surgeon to familiarising himself with the gross features of different tumors.

Breast :—It is of utmost importance that the surgical specimen of a radical mastectomy be so sectioned and so studied that when the examination is completed, the extent of the tumor, the character of its local invasion, the distribution of its metastases (thereby its prognosis) is known. The specimen should first be oriented so that the tumor could easily be located. The nipple and the areola should be carefully examined and the presence or absence of ulceration and edema of the skin should be noted and described.

Dissection should start with the axillary lymph nodes. At times, nodes are located between the pectoral muscles. They should always be looked for, as they may be the only ones involved. In our experience, nodes are found most easily by palpating small amounts of axillary fat.

A curved pair of scissors facilitate the dissection of the lymph nodes. By this means it is even possible to remove nodes as small as 5 mm. in diameter. Examination of the axilla should never be rushed. It is true that the search for nodes is time consuming, but the information obtained is a very valuable one from the point of view of prognosis, for the metastatic involvement of the axilla in cancer of the breast is probably the most important event in the prognosis. The probability of a five year cure after radical mastectomy without axillary involvement is 57 per cent. After the appearance of metastatic deposit in the nodes, with the same operative procedure, the five year cure rate is 20 per cent.

The gross appearance of the nodes varies with the presence or absence of tumor and of inflammation. If the nodes are negative, and with no inflammation, they are often small. When the primary tumor is ulcerated and inflammed, then the axillary nodes are enlarged and hard, even though they may not contain metastatic deposits of carcinoma. Sharply marked out greyish opaque areas within nodes almost always represent metastatic carcinoma. If there are obviously involved lymph nodes, then the microscopic examination of one of such node suffices. On the other hand, if there is any doubt, on naked eye inspection, regarding the metastasis, then it is absolutely necessary that all the nodes should be sectioned and examined under the microscope.

Next, the pectoral muscle should be removed and one should ascertain whether or not the main ducts of the nipple are dilated and whether the tumor is involving that area. The primary tumor should be measured in three dimensions and its relation to skin, nipple, areola, pectoral fascia and the quadrants of the breast should be noted. By methods of step sections of the tumor, including the overlying skin, it becomes easier to observe individual characteristics of different areas in the tumor. There should be other sections too, for instance, from the transition points between apparently involved breast tissue and the diseased area. If the tumor arises in proximity to the nipple or if it has extended so as to involve the pectoral fascia, appropriate sections of the areas should be selected for microscopical study.

The spread of the disease to the lymph nodes and the surrounding tissues is charted and correlated with microscopic involvement (Fig. 1).

Rectum :—The large intestine is studied according to a plan suggested by Duke. First the entire specimen is drawn to scale preferably on a graph paper. The glands are charted on a natural size drawing, numbered, and those which suggest involvement with naked eye inspection are indicated as in (Fig. 2). This involvement of the lymph nodes should subsequently be checked by microscopical examination. Measurement should be taken of the specimen before it is put in a fixative. These measurements consist of the length of the specimen, the size and situation of the tumor together with the amount of free margin of the bowel above and below it. Then the specimen is incised along the middle line anteriorly and stretched out, stitched and tied on a glass frame (Fig. 3). This is a very good method as it retains the length of the bowel and can as well be used for a specimen of carcinoma of the esophagus, stomach and small intestine. The specimen stretched on a frame like this is immersed for one or two days in a jar containing formalin saline. When it is properly fixed, the specimen is taken off the frame and photographed. The growth is then sectioned through what appears to be the point of maximum penetration of the bowel wall by the growth, or at the point of deepest ulceration. A few more transverse slices will enable to arrive at a decision whether the growth has or has not extended through the muscular wall of the rectum and into the pararectal tissues. Direct spread in or through the rectal wall can usually be well judged by naked eye inspection (Fig. 4). Next, a dissection is made of the lymphatic glands which are found in the peri-rectal fat and accompanying the superior hemorrhoidal vessels. Thus, the specimen could be grouped into one of the three groups according to Duke's classification (Fig. 5), so that, even from the gross appearance, it is possible to tell the prognosis.

Tongue :—In the case of an anterior tongue carcinoma where a hemiglossectomy has been done, parallel slices 2 mm. in thickness (Fig. 6) are cut and when reconstructed give a three dimensional idea of the spread of the neoplastic process. This method of serial sections helps in locating the spread of the disease and also to determine whether the line of incision is free from the tumor. In figure 7, the section marked with an arrow shows that the tumor is at the cut edge of the surgical dissection. This distance from the tip of the tongue could easily be measured by counting sections ; section marked 1, being the first near the tip of the tongue. This gives very useful information to the roentgenologist, as it is at this point where the tumor has remained behind in the body, that the post-operative radiation is most indicated.

Lymph Nodes :—An intact node removed in the operation theatre should be immediately put in formalin saline. After three hours fixation, the node should be bissected through the hilum in a plane parallel to the long axis and fixed for 24-28 hours in Bouin's fluid. Very large nodes may be cut in parallel slices 0.5—1 cm. thick in order to ensure adequate penetration of the fixative. If the nodes are incised without preliminary fixation, there may be shrinkage and distortion of cellular pattern.

Uterus :—It should be opened anteriorly. The opening of the uterus is facilitated by the insertion of a probe in the uterine cavity (Fig. 8). The incision, as it reaches the fundus, should be extended in either cornu (Fig. 9), and the specimen be put in a jar containing 10 per cent formalin saline.

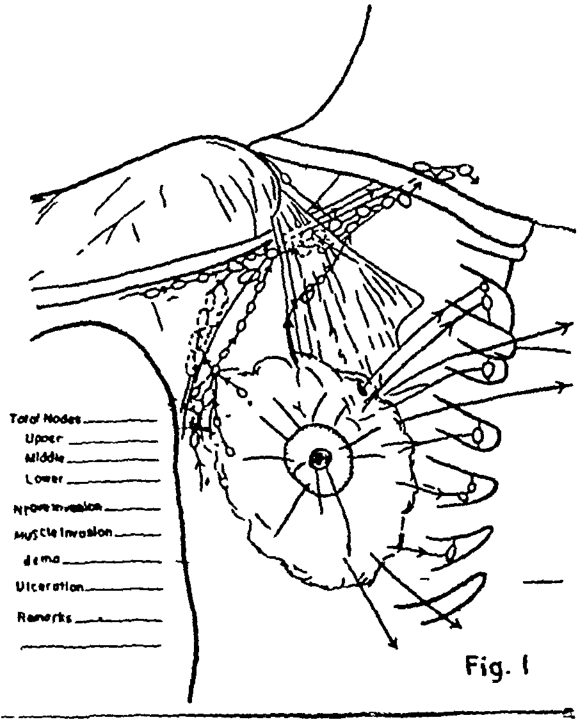

Fig. 1

Fig. 1.—Diagram showing the breast and surrounding structures and lymph node involvement.

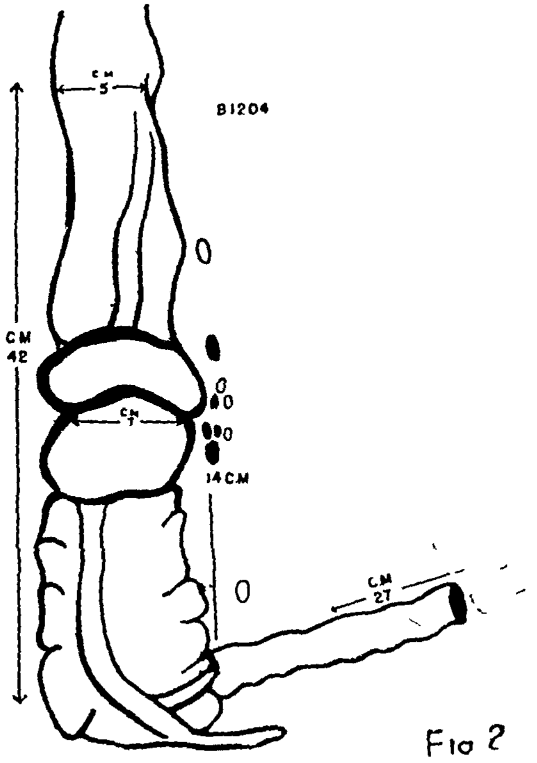

Fig 2

Fig. 2.—Chart for noting involvement of the rectum and its lymph nodes.

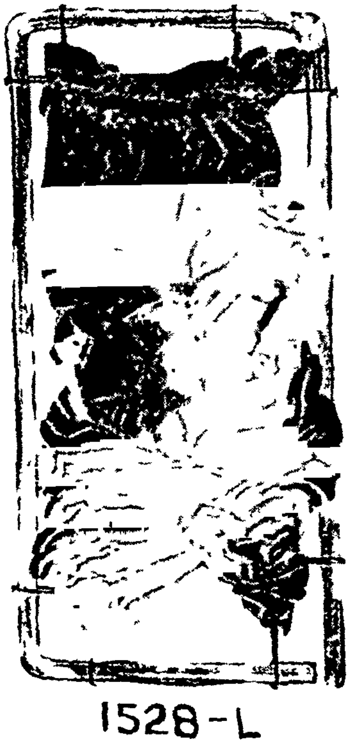

Fig 3

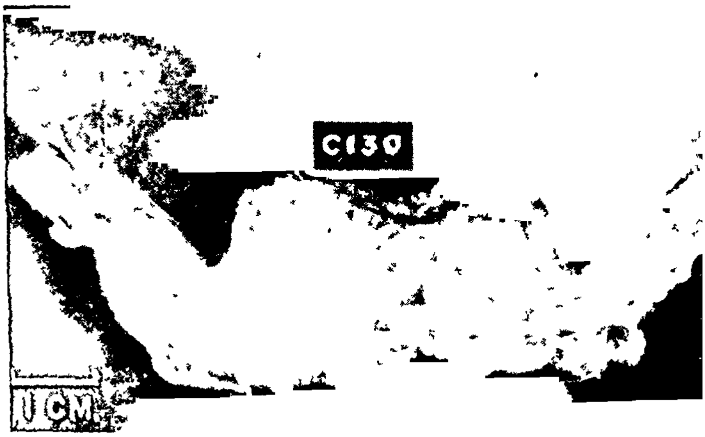

Fig. 3.—Photograph showing the mounting

Fig. 4.—Photograph of a specimen for naked eye

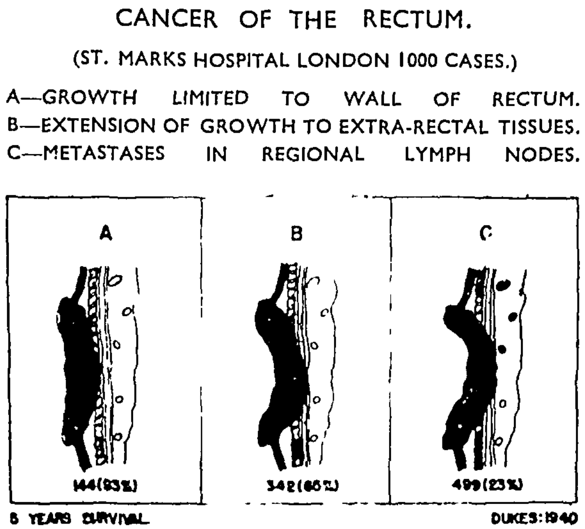
CANCER OF THE RECTUM.
(ST. MARKS HOSPITAL LONDON 1000 CASES.)
A—GROWTH LIMITED TO WALL OF RECTUM.
B—EXTENSION OF GROWTH TO EXTRA-RECTAL TISSUES.
C—METASTASES IN REGIONAL LYMPH NODES.
A
B
C
144(93%)
342(66%)
499(23%)
5 YEARS SURVIVAL
DUKES:1940

Fig. 5

Fig. 5.—Classification of cancer of the rectum (after Dukes).

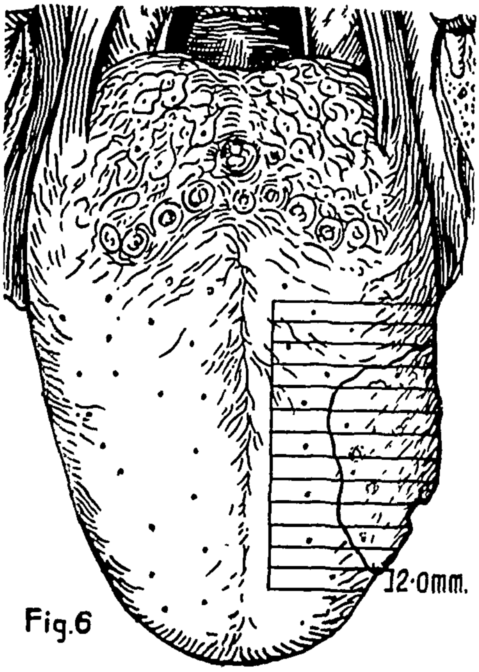

Fig. 6

Fig. 6.—Diagram to show how sections of the tongue are to be taken.

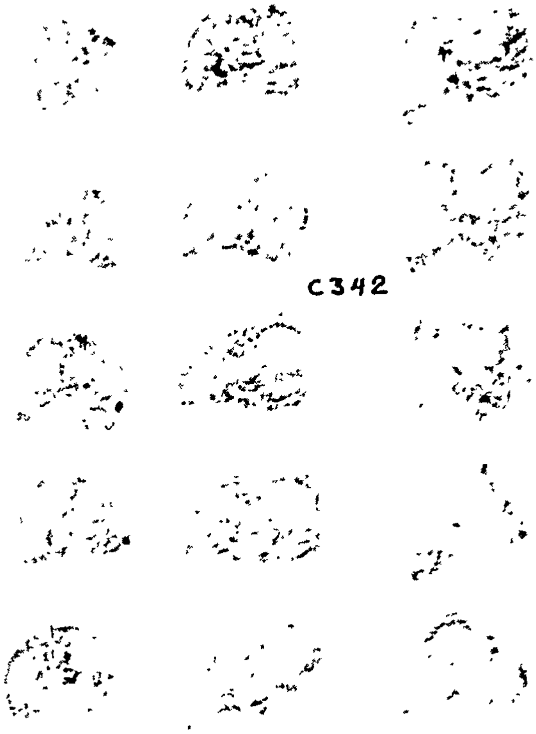

Fig. 7.—Multiple serial sections of the tongue.

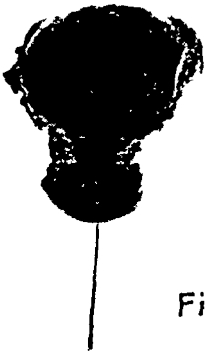

Fig. 8

Fig. 8.—Photograph of a uterus with a probe in the cavity before section.

Fig 9

Fig. 9.—Photograph showing how the

Bones :—Surgical specimens which are brought to the laboratory from the operation theatre consist mainly of amputated or disarticulated limbs of patients suffering from bone sarcoma. In order to facilitate the cutting of sections from such tumors, it is a great advantage to possess an electric saw which would enable complete sagittal sections. Such sections are best obtained when checked with roentgen pictures. Half the portion may be kept for museum mounting, the other half should be subjected to transverse serial sections. These should not be more than 3 mm. in thickness. A representative bit showing a portion of tumor should be taken for processing.

Decalcification of Bone :—Fix the tissue in the Muller's fluid for 4 days: (Potassium bichromate 2—2.5 Gm., sodium sulphate 1 Gm., distilled water 100 cc.). Wash it over night. Treat with the following solution till such time as the tissue becomes soft (10 per cent formalin 90 cc., nitric acid—10 cc.). Subsequently treat it with potassium alum 5 per cent for 24 hours. Wash over night—Dehydrate—clear in grading percentage of alcohol and xylol. Prepare a paraffin block. Cut sections and stain with hematoxylin and eosin.

Operative specimens narrated above comprise the bulk of tumor material that comes to this laboratory. The success of histological diagnosis depends largely on the knowledge in the selection of the pieces to be examined. The pathologist has definite limitations and responsibilities. He is responsible for the proper handling of tissue after it reaches the laboratory. He can only diagnose from the tissue submitted to him. If this tissue is poorly selected and does not reveal a tumor, it is not his responsibility. If a negative report is given, then a false sense of security may be engendered in the mind of the physician who submitted the inadequate material. The pathologist who will give the best diagnosis is the one who not only has adequate material, but has all the pertinent data regarding the patient on whom the biopsy had been made. He should know the name, the age, the sex of the patient. the duration of the disease, the exact location of the lesion, its size in relation to other organs, and all details of previous treatment. The hospital chart should be available for his perusal and, if he so desires, he should have facilities to examine the patient. It should be realised that there are definite limitations to diagnosis on the basis of morphology alone but with all the information and with clinical experience in the evolution and biologic behaviour of tumors, the chances of a correct diagnosis will be enhanced.

ACKNOWLEDGMENT

The main plan of the study of surgical material in the laboratories of the Tata Memorial Hospital has been drawn and worked out under the direction of Dr. V. R. Khanolkar. My thanks are due to him for valuable suggestions in the writing of this paper.

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THE MORAL FACTOR

In the fundamental clash between great nations when their existence is at stake the issue is determined by moral and not by intellectual factors. The part that character plays in medical diagnosis is not always appreciated. It is the quality which allows judgment to be exercised irrespective of worldly considerations which may snare the feet of the lighter breed of doctor.

LORD MORAN (b. 1882).

FIRST THINGS FIRST

Physicians ought to console their patients even if the signs of impending death seems to be present. For the bodies of men are dependent on their spirits. In treating a patient let your first thought be to strengthen his natural vitality. If you strengthen that, you remove ever so many ills without more ado. If you awaken it, however, by the remedies that you use you always work harm. The patient who consults a great many physicians is likely to have a very confused state of mind.

RHAZES, (850-932).

TECHNICAL LIMITATIONS

There were Ophthalmoscopes and Rhinoscopes and Otoscopes and Laryngoscopes and Stethoscopes ; and Thermometers and Spirometers and Dynamometers and Sphygmometers and Pleximeters; and Probes and Probangs and all sorts of frightful inquisitive exploring contrivances; and scales to weigh you in, and tests and balances and pumps and electro-magnets and magneto-electric machines ; in short, apparatus for doing everything but turn you inside out.

OLIVER WENDELL HOLMES (1809-1894).

PLAUSIBILITY

A physician that has his tongue well hung, and is master of the art of persuading, fastens, by the mere force of words, such a virtue upon his remedies, and raises the faith and hopes of the patient to that pitch, that sometimes he masters difficult diseases with the silliest remedies ; which physicians of greater learning could not do with nobler remedies, merely because they talked faintly, and with a soft dead air.

GEORGE BAGLIVI (1668-1706).

PSYCHIATRIC NURSING *

J. C. Marfatia †

It is increasingly realised that no disease in medicine can be called wholly "organic" or wholly "mental." Practically all physical illness has associated mental and emotional aspects and vice versa. Mind and body are not separate entities. They are closely inter-related, inter-dependent and inter-woven with each other. Hence any health programme which does not include the problem of mental health cannot be considered complete.

The above remarks apply to Nursing also. Psychiatric nursing is a neglected subject and is practically unknown in our country. The following remarks may be quoted in this connection—"The Committee found that there was a regrettable lack of training in mental nursing in India, and, at present, no means exist of obtaining a registrable qualification in this important branch of the nursing profession. Some few nursing sisters had obtained the certificate of the Royal Medico-Psychological Association (R. M. P. A.) at an examination held some years ago at Ranchi, but the Committee thought it unlikely that there were many other recipients."[4]

It is not surprising that the attitude of the public towards the mentally afflicted—*viz.*, one of deep-seated prejudice and superstition, is reflected in the attitude of nurses towards their mental patients.

While working in a general hospital, it is painful to see nurses screwing up their noses whenever they have to deal with mental cases and still more painful to see their keenness to transfer a mental case to the psychiatric side as soon as possible. Till such time as the transfer is brought about, the patient in question seldom fails to get a feeling that he is rejected because he is different from other patients. It is a well-known fact that house-physicians and post-graduates have a tendency to pick up the bedside manners and attitudes of their chiefs. Nurses and ward sisters are no exceptions. If physicians (and surgeons) show a sympathetic and understanding attitude towards their mental patients, their subordinates, *viz.*, house-physicians, post-graduates, ward-sisters and nurses, will follow suit. It is significant to note in this connection that many nurses do not even know that psychiatric nursing constitutes an important and specialised branch of general nursing.

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* Based on a lecture delivered for the Refresher Course for Trained Nurses Association of India. (5th Nov. 1951).

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THE POSITION OF MENTAL NURSING IN OTHER COUNTRIES

In foreign countries, psychiatric nursing is considered as a specialised branch of general nursing. A recent survey of the mental health services by Blacker[1] takes the view that the future of the psychiatric services in England will depend almost as much on the selection and training of mental nurses as on the quality of psychiatrists. "According to information provided by the Board of Control, there were in 1938 about 21,600 nurses, trained and others, in mental hospitals in England and Wales. No corresponding figures are available for mental deficiency institutions. We have therefore assumed, on the basis of the number of beds, that there were in 1938, as at the end of 1945, approximately 3,400 nurses of all kinds in mental deficiency institutions in England and Wales. The true figure may possibly have been less in view of the increase in occupied beds since 1938. The total nursing strength of mental hospitals and institutions in England and Wales in 1938 has, therefore, been estimated at about 25,000. If the ratio of trained to other nurses was similar in 1938 to what it was in 1946, the figure of 25,000 includes about 13,400 trained nurses. If we add the 1938 figures of nursing strength in Scottish mental hospitals and institutions, *i.e.*, 1,900 trained and 2,400 other nurses, the totals for Great Britain amounted to about 15,300 trained and about 14,000 other nurses."[3]

"........A mental nurse could qualify either by passing the examination of the Royal Medico-Psychological Association or those of the General Nursing Councils for the supplementary mental registers. In 1943, according to the Horder Report (p. 26) about 45,000 nurses held the certificate of the Royal Medico-Psychological Association as compared with about 10,600 who were enrolled on the mental registers of the General Nursing Councils."[3]

"At the end of 1945 there were rather more than 26,000 nurses in mental hospitals and institutions in Great Britain. Of these, some 14.2 thousand were trained, about 6.4 thousand were students and 5.7 thousand were assistant or other nurses. Roughly, half the total number of nurses were males, but there were 8.5 thousand trained male nurses as compared with 5.7 thousand female."[3]

In other countries, conditions of mental nursing are raised to the same level as those of general nursing and steps are taken to bring the mental nurse into closer alignment with that of the generally trained nurse.

It has been proposed[3] that in the common period, eight weeks would be spent in learning the principles of psychiatric nursing. Students would be introduced to the milder types of mental disability in children and adults from a social and preventive standpoint, leading on gradually to the study of psychosis. As in the other fields, the optional period of six months would be spent in intensive preparation for psychiatric nursing.

Nursing has always been regarded as more or less the exclusive province of women except in the Services and in the mental field. The services of male nurses are extensively utilized for male patients in mental hospitals abroad.

QUALITIES OF A MENTAL NURSE

Mental nursing should be regarded as a specialised branch of general nursing. A mental nurse should have qualities which make an ideal general nurse plus some other important qualifications. She should not only have good physical health but also good mental health, so that she can endure the heavy responsibility and constant strain. She should be emotionally mature. She should be free from the common tendency to poke fun at the mental cases and be capable of considering a mental patient as a sick person just as much sick as a patient with typhoid fever, pneumonia, appendicitis or fracture. Her patience and forbearance will be tested to the utmost degree. She must have the capacity to be able to put herself in the patient's position and thus appreciate what the patient is going through. She must be tactful and resourceful. A spirit of cheerfulness, willingness, obedience, unobtrusiveness and firmness are other essential qualities she must possess. Arguments with patients should be avoided particularly with those subject to delusions. She must not take offence at what the patient does or says, no matter how personal it may seem,because mental patients cannot be held responsible for their actions.

PSYCHIATRIC NURSING

In no profession, except perhaps the Medical and Legal, is there such an excellent opportunity for studying human nature as in Nursing. During illness, different people react in different ways. If there is psychiatric insight, *i.e.*, knowledge of mental dynamisms with which people attempt to deal with their difficulties, she will find that in a surprising number of cases the principles of mental hygiene and of psychiatric nursing may be applied. Her training enables her to recognize the secondary gains the patient obtains from his illness, to correct the faulty attitudes of the relatives in so far as they are directly or indirectly responsible in causing or maintaining his symptoms, and to allay fear and apprehension before an operation by explaining each step in preparation for the anesthetic and operation.

One of the most important functions of a psychiatric nurse is to observe accurately the appearance, behaviour and conduct of patients—the "A B C" of her work. The observations she makes are :

State of emotions or variations of emotions—Is he cheerful, over-happy, downhearted, depressed or despondent'?

Fearfulness, agitation, apprehensiveness, withdrawal, apathy, excitability, violence, destructiveness, orientations, mutism, speech disturbance, thought disturbance, delusions, hallucinations, preoccupation, postures, resistance, refusal to eat, other forms of negativism, sexual behaviour, sleep disturbances, *etc.*, are other observations which may be made.

SOME TYPICAL PSYCHIATRIC CONDITIONS

Paranoia :—Avoid arguing with the patient. A patient with persecutory delusions should not be wilfully deceived as to the purpose of hospitalization, as he immediately becomes suspicious, hostile, resentful and distrusting. He must be told that he is in the hospital for observation and care—that he is among friends who will treat him kindly. Otherwise a paranoid may conclude that his hospitalization is part of a conspiracy. While he may not be told the entire truth he should never be told an untruth. Paranoia is one of the most dangerous forms of insanity because it is so commonly associated with homicidal impulses. If his delusion takes the form that his food is being poisoned by the nurse, he may perpetrate an homicidal attack on the nurse. It is advisable to avoid the subject of their delusions. The danger is all the more because the patient may be able to conceal the existence and nature of the delusion, which will make it impossible to forecast who the victim may be, or the mode of the attack.

Acute Mania :—It is one of the mental diseases which will be an excellent test of a nurse's judgment and resourcefulness. Much tact, endless patience and untiring vigilance are necessary. Force to secure obedience will be absolutely useless. A struggle might lead to injury to either the patient or the nurse. Seclusion and confinement of the patient will not help. Sedatives and, in some cases, restrictions are necessary to prevent the patient from going into a state of acute exhaustion and peripheral circulatory failure. The wet pack and continuous flow bath are valuable sedative measures; these baths have not only a soporific effect but also assist in the elimination of toxins through the skin. Heavy sedation should be avoided as far as possible. Cases of ordinary acute mania, although they cause much concern to near relatives, are the most favourable from the point of view of prognosis.

Depressions :—In depressions of any variety, *viz.*, the depressive phase of Manic-Depressive insanity, or Involutional Melancholia or, Reactive Depression, the greatest danger is that the patient may commit suicide. All melancholics are potential suicides. Various methods are employed by patients and the precautions to be taken in dealing with these types of cases are a very important feature of mental nursing. Some very important rules in the nursing of these patients must always be borne in mind.

1. As far as possible the patients should always be warded on the ground-floor so as to prevent them from committing suicide by jumping out of the window if they are placed on higher floors. He may throw himself headlong from a staircase or some other height.

2. Suicide is more likely to take place during the period when the patient is recovering and not when the depression is acute. The reason is that during the acute stage psychomotor retardation is so extreme that it results in complete inactivity.

3. The patient should never be allowed to be out of sight for even a minute. If suicide occurs at a time when the nurse was not present, or the patient has succeeded in evading her vigilance, that nurse is likely to be held responsible for the unfortunate incident. The patient should never be left alone. The watching is done as unobtrusively as possible so as not to irritate or annoy him by giving him a feeling that he is being relentlessly policed. They should not be allowed to go to the bath or toilet unsupervised.

4. The patient may assume an air of cheerfulness or improvement which might induce the nurse to relax her vigilance and thus secure an opportunity for suicide.

5. The room and clothing should be searched for articles for suicidal purposes frequently but unobtrusively. Care should be taken in permitting the use of sharp or cutting tools. Forks, knives, spoons, *etc.*, must be accounted for after dinner. String, cord or tape should not be in their possession. The patient may improvise a rope from garments or bedsheets.

6. All medicines, disinfectants, *etc.*, are to be kept under lock and key.

Suicide may also occur in cases of epilepsy, G. P. I., some cases of schizophrenia, alcoholics, some cases of paranoia and feeble-minded individuals.

It should be remembered that a melancholic may commit homicide by killing his near relatives first, very often his wife and children, and then committing suicide. The reason he states in the note which is left behind is that he would not like his wife and children to suffer after his death by their having to beg or work hard for their livelihood.

Another problem in the nursing of depressive cases is the refusal of food. Very often tube-feeding becomes imperative. A careful note should be made of the actual amounts of food taken.

The surroundings should be as cheerful as possible and every effort made to make them feel that they are going to get better and that life is worth living.

RECREATION AND OCCUPATION

For both mental and physical well-being, occupation and recreation at appropriate intervals are absolutely necessary. The value of occupation as a therapeutic measure to aid convalescence is being increasingly realized. Keeping a person occupied prevents day-dreaming and introspection. Convalescence is an important and crucial period as this is a period of doubt, loneliness and longing. The percentage of social and psychological recoveries are in direct proportion to the individual attention a patient gets. The patient is encouraged to resume the direction of his own affairs in so far as his ability will permit. Suitable occupation *i.e.*, work fitting to the particular needs of the individual and graded to the capacity of the particular individual in a system of organised occupations, keeps the patient interested, less destructive and enables him to divert his thoughts into more useful channels.

It is easier to have a separate department for occupational therapy in a mental hospital than in a general hospital which has only a few in-patient psychiatric beds. The utmost that one can do by way of occupational therapy in a general hospital is to give patients ward work, for example, cutting cotton-wool, gauze and lint pieces, helping the nurse to make beds or helping her in the pantry or in cleaning the ward. A convalescent patient may even help the nurse in attending to another patient who is newly admitted. This certainly bolsters up his ego and re-establishes his shattered morale. Care should be taken in choosing the type of work which would best suit the patient.

In a mental hospital where one can have a separate department for occupational therapy, occupations like painting, music, sculpturing, games, athletic sports, arts and crafts, dancing, carpentry, basket-making blanket-weaving, rug-making, knitting, *etc.*, can be introduced. Some patients may be encouraged to work in kitchens, laundries, on the farm and in the garden. Cards, chess, parties, concerts, competitions, dramatics, *etc.*, should be provided by way of recreations.

Absolute co-operation of the staff as a whole is essential if occupation therapy is to be a real success. It is also possible then, to have proper classes or groups according to the mental state of patients. A change of occupation may become necessary according to whether the patient is improving or deteriorating.

CONCLUSION

The comparison of psychiatric nursing in India and abroad makes a sad contrast. It is time some beginning is made in our country in the direction of having mental nursing as a specialised branch of general nursing. A course of at least 10 lectures on psychiatric nursing should be added to the nursing curriculum and, for specialization, at least a period of 6 months of intensive training, after having obtained the final diploma in general nursing, would be necessary.

An over-all effort should be made to promote socialized habits and a wholesome interest in reality, stimulating and socializing recreations, which divert feelings, thoughts and activities away from self and toward reality.

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SPECIALISTS

A young medical man who runs off into a speciality, honestly believing that a human organ can be studied and treated separately, like the wheel of a watch, has not intellect enough to be a physician, and ought to have been discouraged from entering the ranks. He who undertakes it from mercernary motives ought to be frowned down, and told that his tendencies and faculties belong to the places where they sell their wares and souls for lucre, and call it business, not a sacred vocation.

ABRAHAM JACOBI (1830-1919).

INTEGRATION

All sciences are connected ; they lend each other material aid as parts of one great whole, each doing its own work not for itself alone, but for the other parts, as the eye guides the whole body and the foot sustains it and leads it from place to place. As with an eye torn out or a foot cut off, so it is with the different departments of knowledge ; none can attain its proper result separately, since all are parts of one and the same complete wisdom.

ROGER BACON (1214-1294).

A technique is described for visualizing the renal parenchyma by the rapid intravenous injection of a large amount of contrast medium. The procedure is similar to that for angiocardiography. After testing for iodine sensitivity, 50 cc. of 70 per cent diodone is injected into an antecubital vein within 2 seconds, and serial films are taken of the renal area. The opacification of the renal parenchyma, and sometimes of the abdominal aorta and renal vessels as well, takes place between 6 and 60 seconds, and is usually at a maximum at about 15 seconds after the injection. Satisfactory nephrograms were obtained in 29 out of 35 patients subjected to the procedure. Its clinical applications have yet to be worked out. World Abstract of Med. **10** : 251, 1951.

BOOK REVIEWS

Price List, E. Merck.—A Price List of the original Pharmaceutical Specialities of E. Merck, Darmstadt, Germany, has been received from their sole agents for the Indian Union—Messrs. Capco Limited of Meher House, 15, Cowasji Patel Street, Bombay.

It gives the prices and packages of all the products with their original trade names of the German Company.

J. C. Patel.

Vademecum Lederle.—The Vademecum of Lederle Laboratories, published by their Indian Company gives the history of its growth during the last 40 years, from a biological laboratory to its present stage. It has now a pharmaceutical section, chemical section and an animal industry section. Besides that, it has a large research organisation of the highest caliber. It is situated at Pearl River. The research is carried out not only in medical pharmaceuticals but also in other divisions like chemistry, physics, biology, and any special technical problems. The Company gives Research fellowships throughout the United States and other parts of the world.

The most recent discoveries of the Research Organisation are folic acid and aureomycin.

The Vademecum consists of all their products—their indications, administration, precautions and packages. It has a therapeutic index where the use of a number of their products is given. Besides that, poisons and their antidotes, obstetrical table, miscellaneous data, and common abbreviations are given.

Besides being useful as a guide to their products, it is of interest on the office table of a doctor.

J. C. Patel.

Pharmacopoeia Internationalis, Editio Prima, Volume I., Price 35/- $5.00, Sw. fr. 20.

Volume I of the first International Pharmacopoeia is just published by the World Health Organisation, Geneva. It is based and resembles British pharmacopoeias in general. It contains 406 pages, 199 monographs and 43 appendices in which reagents, test solutions, biological assays, limit tests, etc. are prescribed. Each monograph is based on the same line as a British pharmacopoeia. It contains mainly the drugs of long established therapeutic value common to a number of British pharmacopoeias, and includes new drugs which seem to be accepted for future pharmacopoeias. Monographs on injections, sterility tests, the pyrogen test, certain tinctures and tablets are promised in Volume II, and also other items where agreement has not been secured.

The language is still Latin and a number of important synonyms are mentioned. Botanical nomenclature accords with the International Rules of Botanical Nomenclature 1935, while for chemistry the system of the International Union of Chemistry has been followed. A system of designating sieves has been taken from reports of the International Organisation for Standardisation.

A number of differences in names can be mentioned like 'liquor' is not used but the term 'solutio' is preferred. Alcoholic tinctures are referred to as ethanolic tinctures. Tinctures of potent drugs where active principles have not been fixed are uniformly 10 per cent by weight.

Each monograph consists of the name of the drug in Latin; if the drug is a substance of known chemical formula its graphic formula; empirical formula and molecular weight; description of the drug with standards, and limits of purity; followed by statements of solubility tests for identification, limit tests for impurities and storage requirements.

Copies of the International Pharmacopoeia can be had from their agents in Delhi; the price is Rs. 35.

The International Pharmacopoeia aims at unifying the different pharmacopoeias existing in the world and with a hope that when the new editions or new pharmacopoeias are written they will follow this international book. The dosage will then be uniform and in the days of short air travels it will not be difficult for a traveller to get his prescriptions dispensed in any country without great difficulty. The book is of great value for reference in teaching institutions and pharmacological and pharmaceutical laboratories.

J. C. Patel.

Did you know that :—

The following personalities are unsuitable for a medical career? (1) "The extreme introvert who lives within himself, and neither desires nor seeks warm friendly relations with people." (2) "The youngster who continues to wage an adolescent rebellion against his family long after his classmates have worked through this stage of development." (3) "The arrogant cocksure chap who is so certain of himself as the epitome of perfection that he is unable to accept criticism or suggestion from faculty or fellow-student." (4) "The insecure person, totally lacking in self-confidence."

Did you know that :—

"The painful stimuli have hemostatic effect. The acceleration of blood clotting time was most marked in 10 to 20 minutes in dogs and rabbits after infliction of painful stimuli." (World Abstract of Med., **10** : 255, 1951).

"......The G. P. is able, if he wishes, to practise medicine in a spirit just as idealistic and just as scientific as the Hospital doctor. In his close and prolonged relationship with patients in their own unregimented surroundings he has something which is more interesting to most men than "the fascinating case" (although the fascinating case turns up in no particular shortage). Paper work is really not so overwhelming....The awkward patient is the exception, not the rule. The limits of General Practice are defined much more by the ability of the doctor than by the incursions of Health Service administration, the need for machines or the widespread reverence for specialists." (Lancet **2** : 1067, 1951).

Believe it or not !!!

"A former instructor in philosophy and novitiate in a monastery who had only brief medical experience as an orderly in an eye and ear infirmary in Boston was said to have established a brilliant reputation as a ship surgeon in the Royal Canadian Navy (The Times, November 22). He served in the Canadian destroyer Cayuga in Korean waters and successfully performed various operations such as amputations and removing a bullet close to the heart. According to the Navy's statement nothing has occurred to indicate that he did not possess the competence of a fully qualified medical man : he is nevertheless to be discharged from the Navy for misconduct.
—"British Medical Journal," **2** : 1378, 1951.

D. D. Vora.

CURRENT MEDICAL LITERATURE

MEDICINE

CHLOROMYCETIN IN THE "HEALTHY CARRIERS" OF ENDAMOEBA HISTOLYTICA, Coronel, A. P. : Amer. Pract., **2** : 782-783, 1951.

The author points out the importance of the carrier of amebic cysts in spreading the disease ; and to the small percentage of acute episodes and exacerbations observed in these carriers. The cysts can cause disease in the host and are blamed for the possible increase of the infection in the U.S.A., and more so in Eucador. Infections are more common in the high plateau regions, where the climate is less tropical, but sanitary conditions are poorer, than along the coast.

In hospital practice, the chronic forms of the disease are more common than the acute episodes—the "amebic colon" is seen on roentgenography. "Healthy Carriers" do not always enjoy good health.

Amebic cysts can lodge in the different layers of the large intestine, more often the proximal part.

Here, microscopical alterations occur through which toxins and bacteria might be carried to the liver and more distant parts by the circulation.

The general symptomatology includes lassitude, anorexia, anemia, and gastro-intestinal disturbances. Intolerance to fatty foods and alcohol, and nervousness have also been described.

Local tenderness may be found in the right lower abdominal quadrant, and may be most acute in the region of the appendix.

Chloromycetin was given to a series of 40 carriers of amebic cysts, in doses of 6 to 12 Gm., over 4 and 8 days, respectively. No side effects were observed. Complete disappearance of the cysts from the stools was observed after discontinuation of the drug.

Three patients with bronchial asthma who were carriers of the cysts showed a coincidental disappearance of the asthma.

A long series of follow-up examinations were not done because of the complicating factor of almost certain re-infection.

CHARLOTTE DE QUADROS.

SURGERY

ADVANCES IN SURGERY, Balfour, D. C. : The Practitioner, **167** : 343-349, 1951.

Anesthesia :—Advances in this field have vastly increased the scope and progress of surgery. The establishment of departments of anesthesiology has led to intensive investigation into the properties of new anesthetic agents and new methods of administration. The use of curare has a wide range of application and makes possible adequate anesthesia with intravenous pentothal sodium, together with the use of 50 per cent nitrous oxide and 50 per cent oxygen through a Magill intratracheal tube which has proved a great boon to successful and safe anesthesia. One of the most important contributions has been the diagnostic and therapeutic nerve blocks under radiological observation.

Chemotherapy :—In this field almost a new chapter in the history of medicine has been written. The bactericidal and therapeutic indications of the antibiotics have been evolved. The importance of sound surgical practice, which cannot be replaced by chemotherapy and the antibiotics, has been stressed.

Surgery of Cancer :—Definite advances have been made both in the early recognition of the condition by the education of the profession and the public, and in the extension of the scope of surgery in dealing with situations hitherto considered inaccessible. The important contribution of cellular differentiation in secretions which have been in contact with the lesion has enabled a greater percentage of earlier and accurate diagnoses. Endoscopy and roentgenology have vastly helped the early recognition and resectability of cancer of the esophagus. The more frequent use of total gastrectomy has added to the percentage of cures. In cancer of the colon, the most conspicuous advance has been the more frequent employment of one-stage operations which has greatly reduced the mortality. Pneumonectomy has become almost a routine procedure for cancer of the lung. New factors in the development of cancer of the prostate are being sought, as is seen in the work of Huggins who has shown that prostatic cancer is the first example of widespread carcinomatosis where endocrine therapy has a beneficial effect.

Cardiac Surgery :—The experimental laboratory has led to spectacular developments in the surgery of the heart and blood vessels and the correcting of congenital anomalies like patent ductus arteriosus, the tetralogy of Fallot and coarctation of the aorta will be recognised as one of the greatest triumphs of the era.

Pancreatectomy:—The experimental and clinical investigations of Whipple and his associates have opened up a field of definite possibilities. The spectacular cures of hyperinsulinism by removal of islet cell tumours and the partial and total extirpation of the pancreas represent an epoch making event, and may be the forerunner of more frequent surgical intervention in pancreatic carcinoma.

Portal Hypertension :—Though the present status is somewhat uncertain, spectacular results in individual cases have been effected where fatal hematemesis has been prevented.

Peptic Ulcer :—Though many problems are still unsolved and the advisability of radical resection has been questioned, new approaches are still being sought. The introduction of vagotomy has added another tool which seems to be of greatest usefulness in recurrent ulcer after partial gastrectomy. Definite progress has been achieved in the recognition of definite criteria for surgical intervention for massive bleeding in peptic ulcer, and the non-surgical management of perforation has been strongly advocated with results that show that it may well be safer for the patient than surgical intervention.

EUSTACE J. DE SOUZA.

DERMATOLOGY

STREPTOMYCIN THERAPY OF ERYTHEMA INDURATUM, Witherspoon, F. G., and Hamilton, C. M. : Arch. of Dermat. and Syph., **64** : 49-51, 1952.

On reviewing the literature on the efficacy of streptomycin, the authors found the following conditions amenable to streptomycin therapy : lupus vulgaris, scrofuloderma, tuberculosis miliaris disseminata faciei, tuberculous ulcers of the tongue, tuberculosis verrucosa cutis, actinomycosis, tularemia, chancroid, granuloma inguinale and various dermatosis due to *Pseudomonas aeroginosa*. But they did not come across any report on the treatment of erythema induratum with streptomycin and hence report their own two cases. One of the patients was a female aged 36. She had cervical glandular tuberculosis plus ulcers on both calves. They did not respond to the usual mode of treatment with X-rays, *etc.*, for 15 months. Then streptomycin was injected in the dose of 0.5 Gm. twice a day for 42 days. Healing was complete in 10 months. After 3 months, the cervical glands were no longer palpable. The second patient was also a female aged 16. She had indurated erythematous lesions on the posterior surface of the legs just above the ankle. Biopsy confirmed the diagnosis but left behind a non-healing ulcer which was treated with dihydrostreptomycin 0.5 Gm. twice a day for 24 days. The ulcer healed completely after 10 days, leaving behind a hyperpigmented scar. It must be added that streptomycin treatment was employed only after thorough clinical and laboratory investigations of the cases and when conventional therapy had failed. Erythema induratum is an id reaction in the skin due to a tuberculous focus. This focus was present in the first case but could not be traced in the second one. The report is illustrated with photographs of non-healed and healed ulcers.

T. K. MEHTA.

PROGESTERONE THERAPY IN DERMATOSES OF PREGNANCY (Herpes Gestationis): Keaty, C., Jones, P. E., and Lamb, J. H.: Arch. of Dermat. and Syph. **63**: 675-686, 1951.

Though the incidence of pruritic polymorphous eruptions during pregnancy is not very great, yet its study, in the opinion of the authors, is important if the risk to the fetus is to be avoided. The rash may resemble that of dermatitis herpetiformis. It may occur at any time of pregnancy but its onset is greatest during the third trimester as then the production of the chorionic gonadotropin by the chorioplacental system is at the highest. It has been observed experimentally that increase in chorionic gonadotropin is associated with decreased production of progesterone. And this hormonal imbalance suggested to the authors the substitution therapy with progesterone. This substitution therapy has been used with varying success in toxemias of pregnancy where the same type of hormonal imbalance has been observed. Hormonal imbalance was suggested by some as an etiological factor for the dermatosis of pregnancy but Kebra and others considered it to be of toxic origin like other toxemias of pregnancy. The prognosis for the fetus is not good. Intra-uterine death, miscarriage or prematurity and the incidence of fetal anomalies support the concept of toxic etiology.

The authors investigated ten patients with pruritic polymorphic eruptions. In seven, the onset was in late pregnancy. There had been a fetal mortality of 30 per cent in the course of 20 previous pregnancies. Four of the 10 patients had experienced the dermatosis with previous pregnancies, it having occurred seven times in the 20 previous pregnancies (35 per cent). Fifty per cent of the patients had one or the other symptoms of toxemia of pregnancy. The level of blood chorionic gonadotropin in seven patients was abnormally elevated during the late stage of pregnancy, averaging 3,125 rat units per 100 cc. of blood (normal, 500 to 750 R. U.) Progesterone as Proluton, 25 to 50 mg. daily by intramuscular injection was administered to patients with a subsidence of the rash in all 10 patients. There was no fetal accident.

T. K. MEHTA.

GYNECOLOGY

MENOPAUSAL SYNDROME, H. Rogers, L.: Med. World, **75**: 377, 1951, 12 references.

The author advocates treatment of the symptoms of the menopause whether due to natural ageing of the ovaries, surgical intervention, or irradiation—with a view to alleviating them, with minimal stimulation of the uterus and breasts.

The cause of the symptoms is somewhat obscure. They are induced by a lowering of the estrogen blood level. along with an increase in the pituitary gonadotropins circulating in the body and being excreted by the kidneys. It has been shown conclusively that elevated gonadotropins are not responsible for these symptoms and it is known that women obtain symptomatic relief from the administration of naturally occurring or synthetic estrogens, without a depression of urinary gonadotropin level.

Symptoms :—The hot flush is pathognomonic of the menopause. It usually starts as a feeling of hot-fullness in the epigastrium spreading through the chest to the arms and face and head. It may be a definite flushing, followed by perspiration, and it may last from a few seconds to a few minutes. Other disturbances are :—Subjective nervousness, menstrual disturbances, excitability, depression and crying; irritability, fatigability and lassitude ; disturbed sleep ; tachycardia, palpitation an pseudodyspnea ; vertigo and scotomata ; impaired memory ; headache ; frigidity, numbness and tingling in the hands and feet ; occipito-cervical aching ; and sweating.

The treatment is palliative—enough to ease the symptoms but not to eliminate them completely. Estrogens are effective, but some cases require high doses—high enough to produce breast stimulation and endometrial proliferation. On account of this, they have, in the last few years, been combined with testosterone. (Androgens have also been used to relieve menopausal symptoms, but usually produce masculinising signs). Estrogens and androgens modify the specific action of each other but do not neutralise each other. The virilising signs—mild hoarseness, acne and hirsutism occur along with vaginal bleeding, maturation of the vaginal cells and breast engorgement, but the latter are never excessive.

The author believes that the majority of women do well with small daily oral doses of estrogens, but, for selected cases, the combined hormones are better.

Three types of hormone combinations are available :—(1) Conjugated equine estrogens and methyl testosterone; (2) Diethylstilbestrol and methyl testosterone ; (3) Estradiol and methyl testosterone.

The author advocates the use of 0.5 mg. estradiol with 5.0 mg. methyl testosterone daily for the relief of symptoms. The patients must report frequently so that the dose may be adjusted. If virilisation (change of voice) occurs, estrogens alone are substituted for the combination until these changes disappear.

The combined hormones also help in restoring and increasing libido, and are therefore particularly useful in surgically castrated young married females and in frigidity. In ageing cases, with involutionary changes, libido is restored to its menopausal level.

The combined hormones are also of value in women with senile post-menopausal osteoporosis.

The complications that have been noticed with combined hormones are vulval hyperemia and a flare-up of senile vaginitis. Sodium retention with ankle edema has also been noted.

The author believes that the combined hormones should be used in those cases where such high doses of estrogen are required that bleeding or other unpleasant side effects would occur. Estrogens alone should be used when small doses of the hormone give relief.

CHARLOTTE DE QUADROS.

THE VALUE OF THE ENDOMETRIAL BIOPSY, Hampson, F. : Med. Press 5854 : 60-64, 1951 : 4 figures, 13 references.

The author tells us of the value of the biopsy specimens obtained by endometrial curettage, as a means of assessing the condition of the endometrium, as well as that of ovarian activity in the light of the endometrial response to ovarian stimulation.

The Normal Cyclical Changes :—He first describes the normal variation of the endometrial pattern during the four principal stages of the menstrual cycle, beginning just after menstruation has ceased—the early proliferative, the late proliferative, the early secretory and the late secretory phase.

The Value of Biopsy in practice is then stressed in the following conditions :—

Sterility : A biopsy should be done where clinical examination of the husband and wife, and seminal examination of the husband have failed to show a reason for the absence of conception. Attention is drawn here to two conditions which are believed to be responsible for some cases of sterility, and which can be diagnosed only by biopsy-anovular menstrual cycles, and localised endometrial tuberculosis. These two conditions can occur without any other clinical findings. In both cases, the biopsy should be performed late in the cycle. When an anovular cycle is met with, the biopsy must be repeated. The finding of a singular anovular cycle should never be accepted as a satisfactory explanation of sterility.

Other conditions too may be found—hypoplasia, endometritis, or malignancy, but these are not likely to have gone unsuspected.

Irregular Bleeding and Other Discharges :—Endometrial biopsy is carried out, where there is irregular uterine bleeding or other discharge, such as the water fluid suggestive of adenocarcinoma. Where the latter is suspected, a negative finding should be accepted with reserve, as the curette may miss the affected area.

The author also discusses the relationship between the histological appearances—especially that of endometrial hyperplasia—and clinically functional bleeding, and shows the danger of regarding the endometrium simply as an indicator of ovarian function. In a large group of cases, he says, showing functional bleeding, there will be a higher percentage of hyperplastic endometrial pictures than the same number of cases without functional bleeding, but the results of a biopsy in functional bleeding must be accepted with caution.

The second problem discussed is the relationship between endometrial hyperplasia and carcinoma. It is generally believed, now, that in the post-menopausal epoch there is some relationship between the two. In women who have passed the menopause, the finding of a frankly hyperplastic endometrium is an indication for a careful follow-up as an adenocarcinoma is more likely to develop in these patients than in those who do not show hyperplasia.

A chronic discharge is sometimes occasioned by chronic endometritis. The presence of plasma cells, in fair numbers in the biopsy specimen, helps to differentiate chronic endometritis from the normal cellular infiltration that occurs just before menstruation.

The biopsy findings in cases of abortion, hydatidiform mole, and chorioncarcinoma are next dealt with.

The author describes the picture in each case and points out how difficult it is, in certain cases of a typical mole, to state whether or not malignant changes have occurred. The main points in the diagnosis of chorioncarcinoma are, invasion of the uterine wall with trophoblastic cells, destruction of uterine tissue, coagulation necrosis and hemorrhage. Along with these changes, no recognisable villi remain. Where the latter are still present, the diagnosis of malignancy may be extremely difficult. It is important to remember that chorioncarcinoma may arise in the uterine wall and so escape the curette.

In Unexplained Amenorrhea, either primary or secondary, the biopsy may establish the reason. Endometrial hypoplasia, endometrial tuberculosis, and extra-uterine pregnancy are cited as causes of unexplained amenorrhea. In conclusion, the author stresses the value of biopsy in helping to make a diagnosis in local as well as in general conditions. It may well be the only means of doing so.

CHARLOTTE DE QUADROS.

NOTICE TO CONTRIBUTORS

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ILLUSTRATIONS.—Illustrations will not be accepted unless they reach a certain standard of excellence technically, present an attractive appearance and add significantly to the value of the presentation. They are to be referred to in the text by Roman numerals. Legends or captions are to be typed on separate sheets and numbered correspondingly. Line drawings and graphs, which should be about twice their intended final size, are to be carefully drawn in Indian ink on tracing linen, or card board, or stout smooth white paper; blue-lined graph paper of good quality may be used for graphs. Lettering of drawings and graphs must be lightly written in pencil. When half-tone reproduction of X-ray or other illustrations is required the author is advised to send the original film unless he wishes to bring out special points in a print of his own choice. Photographs and photo-micrographs should be printed on glossy paper, should be larger than the size desired for reproduction, and if transmitted through the post in a tube, should be rolled with the picture outside.

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Examples. 1. Coller, F. A., and Maddock, W. G.; The Function of Peripheral Vasoconstriction, Ann. Surg. 100 : 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

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ORIGINAL ARTICLE

STUDIES ON NUTRITIONAL EDEMA

CLINICAL, BIOCHEMICAL AND PATHOLOGICAL OBSERVATIONS

C. Gopalan,* P. S. Venkatachalam,* K. Someswara Rao,* and P. S. Menon*

Edema *of nutritional origin may occur in a variety of clinical states* like wet beri-beri, scurvy, anemias, epidemic dropsy and starvation. This report deals with the condition known as famine edema, hunger edema and sometimes as "hypoproteinemic edema" ; the term "nutritional edema" used here applies only to this condition.

Nutritional edema has been known to occur in times of famine from very ancient times (Porter,[12]). In World War I, with the outbreak of famine conditions over large parts of Europe, there was widespread occurrence of this condition there (Youmans,[17]). Nutritional edema was a common complication among the victims of the Bengal famine (Fitch,[7] ; Bose,[2]). Investigations on the disease received a fresh impetus during World War II, when famine conditions prevailed in many European countries. Several reports of observations on cases arising from war conditions have appeared. (Sinclair,[14] Vaughan, *et al.*[16] and : Netherland Government Report[11]). A helpful contribution to the understanding of this problem and the pathology of the 'famine state' is the controlled observation on starvation in human volunteers in Minnesota, reported by Keys[9]. Cases of nutritional edema are frequently seen in hospitals in South India. Investigations on this disease may be expected to throw some light on many ill-understood physiological and pathological mechanisms.

Clinical Material :—The cases that have been selected for the purpose of this investigation are those of nutritional edema apparently uncomplicated by conditioning factors like cirrhosis, *etc.* The clinical description of this disease here is based on observations on 39 cases. The age distribution of the cases ranged from 17-50 years. All cases, except one, were males. It would be wrong, however, to draw any conclusions as to the true sex incidence of the disease in the general population from these figures. The circumstances attendant on our investigation tended to favour a selection of male cases. However, we gained the impression in the course of our investigation that the condition was more common in males, unlike most other deficiency diseases. The higher incidence of nutritional edema in males than in females has also been referred to by other workers (Sinclair,[14], Netherlands Government Report[11]). The reasons for this sex difference in incidence, if such really exists, are not clear.

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Diet and Economic Status :—Twenty-two cases in this series were destitutes. The others belonged to the poorest section of the population. The former group earned their livelihood mainly by begging. Patients in the latter group had no fixed income. They used to work as and when work was available. The work was mostly manual labour and the daily wages ranged from a few annas to a rupee. The main article of diet was ragi, cholam or rice. Usually, these cereals were cooked and consumed with some salt and chillies. Even this meagre fare was not available to these patients on some days. Vegetables of the leafy or non-leafy variety were an occasional luxury. Pulses and fats were, rarely if ever, included. Milk, butter-milk and meat were completely absent from the dietary. The diet was thus grossly deficient in quality and quantity—in calories and proteins and in most of the other nutrients.

Presenting Symptoms :—The presenting complaints in all cases were 'swelling of the body' and marked weakness. The weakness was so severe that even talking a few words was a great effort and patients would prefer to spend the whole day and night in bed.

A few cases also complained of diarrhea and vague pains in the extremities which were particularly severe while walking. The pains were not shooting or stabbing, but of a dull boring nature. Most of the patients complained that they were feeling very cold even in warm weather and preferred to lie in their beds completely covered with blankets. All the male patients suffered from loss of libido, while the only female subject studied in the investigation complained of very scanty and irregular menstruation. The appetite was good in the majority of the cases, while in six subjects, it was poor. Patients did not complain of thirst.

History of Onset :—The swelling had been present in these cases for periods ranging from 15 to 80 days before admission. The onset of the swelling was always preceded by general weakness and easy fatigueability for several months during which period the patients were unable to undertake any occupation. This was evidently an important factor in the evolution of the disease since, because of this enforced idleness, these patients were unable to earn even the unsatisfactory food on which they were subsisting. All the subjects had been progressively losing weight for several months preceding admission. Some of the subjects had been treated in a hospital for the very complaints they were now suffering from, and had been discharged 'cured' some months ago. Practically every patient gave a history of having suffered from bouts of diarrhea at sometime or other during the preceding months though only ten patients actually had diarrhea at the time of admission. The stools during the bouts of diarrhea were watery, but did not contain blood or mucus. These attacks of diarrhea used to last for a week or more and subside without any treatment. The onset of edema was an insidious process in most cases, taking several weeks. In others, however, fairly severe edema seemed to have set in the course of two or three days ; in these latter cases, there was the history that the patient had previously just recovered either from a severe bout of diarrhea or a short attack of fever.

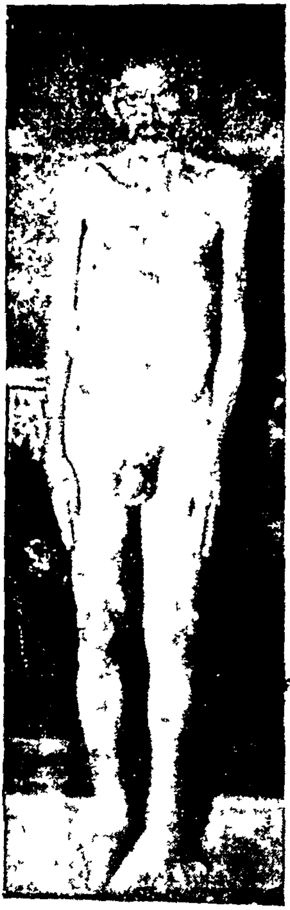

Fig. 1.—Case of nutritional edema, showing the general appearance. Pitting nature of the edema is clearly seen in the legs.

CLINICAL FEATURES

Edema:—On examination of the patients, the most obvious clinical sign was the edema which varied in extent and severity from case to case (Fig. 1). For purposes of investigation the edema was graded as follows: Grade I—swelling involving feet, ankles and lower part of the legs. Grade II—swelling involving thighs and upper extremeties also. Grade III—swelling involving the face and trunk also.

The edema was always maximal in the dependant parts and pitted easily on digital pressure. Edema of the scrotum and penis was not an invariable feature even in cases with extensive edema over other parts of the body. This is probably because the skin and subcutaneous tissue of the scrotum had become tough and thickened from filarial or other infections. Edema of the face and eyelids was seen only in very severe cases ; slight edema of these parts was, however, present even in mild cases, examined after a few hours rest in bed. Ascites of varying intensity was present in 30 cases. All these belonged to the Grade II and III of the above classification. Ascites was never seen in a case with minimal edema, classified as Grade I. Hydrothorax was present in only one subject and pericardial effusion was not seen in any case.

The Skin :—The skin appeared dry and was usually covered with branny scales. Symmetrical pellagrous dermatitis was present over the forearm in one case, while ten subjects showed mosaic dermatoses or crackled skin, over the anterolateral aspects of their legs and thighs. Severe crazy-pavement dermatoses which was present in cases of the nutritional edema syndrome in children, was absent in these adult subjects. In seven subjects there was a dark brown pigmentation of the skin of the face on either side of the nose of the 'butterfly' distribution. In the same subjects, as well as in three others, dark pigmentation was also observed over the knuckles and dorsum of the fingers and the ankles. The skin of the pigmented region appeared thickened and lichenified. A few cases also showed a coarse thickening of the skin of the palms.

Two subjects had impetiginous ulcers on the legs while a third had a large punched out "tropical ulcer" in the leg. These ulcers were refractory even to very energetic treatment with antibiotics in the early stages and began to heal very slowly, only when the nutritional status of the patients was improved with appropriate measures.

The skin was appreciably cold to the touch in all cases ; this was in keeping with the observation that the mouth temperature was usually well below normal in all cases at all times. Sweating was minimal even in warm weather and inspite of patients covering themselves with warm blankets. Evidence of cyanosis was present in several cases at the tips of the fingers and nose.

The Hair :—The hair over the head was dry, lustreless, straight and sparse. The diffuse alopecia was so marked in some cases that wide areas of the bare scalp were visible. Pigmentary changes in the hair of the type seen in children suffering from nutritional edema syndrome, were not seen ; but in all cases the hair had lost its bright lustre. In practically all subjects, the growth of the hair on the face was slow and in several of them scanty. Patients who had not shaved for months had a beard-growth of a few days ; in some the skin over the temples and cheeks was smooth and hairless, and scanty distribution of hair was noticed only over the chin and upper lip. Axillary and pubic hair were appreciably sparse in nine cases.

Prominence of the nipple was present in six subjects. In three of these, the prominence was so great as to justify a diagnosis of gynecomastia. The gynecomastia was unilateral in one case. The case which showed gynecomastia of the maximum degree was a man aged 30 years, who showed a breast development about the size of that of a girl of 15 years (4 inches in diameter).

The sparseness of the sexual hair, the loss of libido and impotence, and the occurrence of gynecomastia, strongly indicate a derangement of sex hormone metabolism. Histological examination of the specimens obtained from testicular biopsy in these cases did show evidence of involvement of the testes and this will be dealt with separately.

Mental Changes :—Mental changes were present to varying extents in practically all cases. In some cases, they were so mild, that without the knowledge of the previous mental state of the patient, it was easy to miss them, but the improvement that set in after the institution of the treatment indicated mental involvement. These mental changes usually took the form of mild dementia. Patients were as a rule apathetic, had a dull facial expression and appeared disinterested in what was going on around. They were unmindful of their clothes and appearance. They could not comprehend simple questions or give a cogent history. Loss of memory for events and names were present in many cases. Some patients were peevish and irritable and were often heard whining unintelligibly ; these patients might perhaps have been violent if their physical condition had permitted it. It was not unusual for patients who had voluntarily sought admission to run away from the hospital and later to come back without apparently any reason. Paranoid delusions were present in one, while in two others, there was a distinct tendency to be moved to tears without provocation. Some patients appeared unduly anxious and worried. There was only one patient in this series who became frankly maniacal. This man actually behaved as a deaf-mute for two or three days after admission ; with the institution of treatment he became gradually increasingly irritable, till on the tenth day of admission he became so excited and violent as to require his being restrained under the sheets. During the maniacal outburst, he seemed to suffer from many delusions.

The occurrence of mental changes in nutritional edema has evidently more than a mere academic interest. These mental changes may seriously interfere with rehabilitation and treatment. They call for much understanding, persuasion and perseverance in the management of these cases.

Alimentary System :—The appetite was apparently good in all but five subjects. Inspite of this, it was very difficult to get many of the patients to take the skimmed milk that was supplied to them. The appetite was often for articles of food which either could not be had or which the patients could not obviously digest. In a few cases, where there was a craving for certain foods, when these foods were actually produced, the patient did not want them. In short, the appetite of these patients was often very erratic and misleading.

Four subjects had glossitis of moderate degree, but in the rest, the tongue and the buccal mucous membrane did not show evidence of inflammation or ulceration. In some severely edematous subjects, the tongue appeared large, and indentations caused by the teeth were visible at the margins. Most of these severely edematous subjects had a characteristic 'thick,' slurring speech, and a low-pitched hoarse voice, which were indicative of defective articulation probably caused by the edema of the organs concerned in articulation and phonation.

Diarrhea was present in ten subjects on admission. In others, it occurred on and off during their stay in hospital. Four of these were the subjects who showed glossitis ; the fifth case had the symmetrical dermatitis in the forearm already mentioned. The diarrhea was unassociated with griping, tenesmus or abdominal pain, but flatulence and distension were sometimes present. The stools were sometimes watery, but did not contain blood or mucus. Culture of the stools in four subjects with diarrhea was negative for pathogenic organisms. Microscopic examination of the stools revealed the presence of ankylostome ova in seven of the subjects and the ova of ascaris in two. This is in marked contrast to cases of the nutritional edema syndrome in children in which over 80 per cent of the cases showed evidence of heavy ascaris infestation.

The occurrence of intestinal parasitic infestation and bacterial infection in cases of nutritional edema must be obviously very much greater than this report indicates. For the purposes of this investigation, complicated cases with conditioning factors in operation were not selected as far as possible. In adult cases of nutritional edema in the plains, a large number of cases are complicated by intestinal infestation with ankylostomes.

Cardiovascular System :—Inspite of the severe edema, the patients never suffered from dyspnea; indeed, the respiratory rate in most subjects was below normal. Patients could lie flat in bed without pillows. Examination of the heart did not reveal any abnormality, except that the heart sounds were feeble and the heart rate was considerably diminished. The neck veins were not prominent and there were no rales at the pulmonary bases. In short, there was no evidence of cardiac failure being even partly responsible for the edema.

Bradycardia was a characteristic feature of these cases; the heart rate being as low as 40 per minute in three cases. In 12 cases the heart rate was below 60 per minute, while there were only 9 cases with heart rates which were normal (72/min.) or above normal. The heart rate increased on exertion, but not to the abnormal levels reported in wet beri-beri.

The blood pressure was uniformly low in all cases investigated. The fall was noticeable in both systolic as well as diastolic components, but was more pronounced in the systolic, resulting in a lowered pulse pressure and a fall in the amplitude of the peripheral pulse. This is in contrast to cases of wet beri-beri where the pulse pressure is considerably raised.

In 19 subjects, the systolic blood pressure was below 90 mm. of mercury, while the maximum pressure ever observed was 110 mm. in two cases. The lowest blood pressure recorded was 70/50 mm. The fall in blood pressure and the bradycardia generally paralleled the severity of the case, but there were exceptions.

These observations on blood pressure are in line with those of Spies and Stone[15] who found that in persons with nutritive failure the blood pressure was below normal and that it rose slowly as the nutritive failure was arrested. These authors further report that after the administration of desoxy corticosterone acetate (DOCA) to three persons with nutritive failure, the blood pressure promptly increased, to drop again after DOCA administration was discontinued. In one of our cases of nutritional edema in which 5 mg. of DOCA was administered parenterally for four days, it was found that the blood pressure rose from 75/55 mm. to 100/60 mm. at the end of four days, while in other cases of nutritional edema which were not treated with DOCA, no change in the blood pressure was noted in four days.

Radiographic examination of the heart done in three subjects revealed a cardiac silhouette which was of either normal or smaller than normal in size. The marked enlargement of the heart characteristic of wet beri-beri was absent.

Two cases had ocular signs of vitamin A deficiency—xerosis and night blindness. With the exception of these, and the four cases that showed glossitis and one case with pellagrous dermatoses, clinical signs of vitamin deficiencies were absent in these cases. This observation is in line with the reported rarity of vitamin deficiency signs in famine areas.

Urine :—Detailed findings regarding the urinary changes are being published separately. Urinary output was considerably reduced in all cases before treatment and it was not uncommon to see patients passing 200 to 500 cc. per 24 hours. In fact, in 80 per cent of the subjects, the output was well below 1,000 cc./24 hours. With the institution of successful treatment, there was polyuria, which was particularly pronounced at night time, when the patients were resting in bed. The initial specific gravity of the urine ranged between 1013—1018, which is perhaps lower than what might be expected considering the oliguria. Apparently the total solids excreted in the urine in these cases are low. In support of this, it was actually observed in these subjects, that inspite of the pronounced oliguria, the concentration of urea and chlorides per cc. of urine was not high.

BIOCHEMICAL CHANGES

Plasma Proteins :—Plasma protein determinations were carried out in 27 cases of nutritional edema using the Kjeldahl method. Twenty-six per cent sodium sulphate was employed for separation of the albumin and the globulin fractions. The results set out in Table 1 show that there was an appreciable reduction in plasma proteins in all cases of nutritional edema. It is necessary to emphasise this in view of Sinclair's[14] observation that plasma protein levels in cases of nutritional edema observed in Europe were normal. The estimations of albumin and globulin fractions indicate that, in all cases, the fall in total protein was almost entirely due to a fall in the albumin fraction. The globulin fraction, on the other hand, was often elevated. Exactly similar findings were reported in nutritional edema cases observed in the Bengal famine (Bose, *et al.*[2] 1946). In view of this, it would seem necessary, in cases of nutritional edema, to estimate the albumin and globulin fractions separately since a fall in the former may be offset by a rise in the latter and thus an erroneous view may be obtained by estimation of the total protein alone. Our observations here with regard to plasma proteins are in line with those of Anderson and Altmann,[1] who estimated the plasma protein fractions in adult nutritional edema cases by the electrophoretic technique. There was no parallelism in these cases between the severity of the edema and the fall in the serum albumin level.

It may be interesting to compare the plasma protein figures in these cases of adult nutritional edema with similar figures obtained in cases of nutritional edema syndrome in children. Reduction of total plasma proteins and of the albumin fraction were also observed in the latter condition. With regard to globulin, however, while in the cases reported here, the level was often above normal, in children with the nutritional edema syndrome, the level of globulin was not appreciably altered (Menon[10]). If the rise in globulin is the result of malnutrition, there seems no reason why it should occur only in adult cases of nutritional edema. On the other hand, if the rise is due to chronic infection or infestation, it is understandable that it should be more often present in adults who have had a longer period of exposure to conditions favourable to such infections than in children.

Plasma Sodium and Chlorides :—Plasma sodium was estimated in 18 cases and the results are shown in Table 1. In the development of edema, sodium retention is believed to play an important part. The results obtained here show that the plasma sodium level in cases of nutritional edema was normal or below normal in all cases. It would be, however, wrong to conclude from this data that there is no evidence of sodium retention. The extra-cellular fluid volume in nutritional edema is considerably increased ; therefore, there can be an absolute increase in the sodium content of the extracellular fluid, though the sodium level per 100 cc. of extracellular fluid may be slightly lower than normal. The figures for plasma chlorides estimated in seven cases were also normal or slightly lower than normal. The high figures reported for plasma chlorides in cases of congestive cardiac failure were not obtained,

TABLE 1.—*Plasma Proteins, Sodium and Chloride Levels.*

Substance estimated.	No. of cases investigated.	Range of values.	Average.	S.D.
Plasma proteins Gm./100 cc. ..	27	3.896 to 6.825	5.208	0.814
Albumin ,, ..	26	1.472 to 4.900	2.803	0.962
Globulin ,, ..	26	1.225 to 3.593	2.361	0.811
Plasma sodium mg./100 cc. ..	18	288 to 373	322	20.47
Plasma chlorides ,, (as sodium chloride) ..	7	458 to 510	492	17.66

Glucose Tolerance Test :—The glucose tolerance test was carried out in nine cases. In two of these, the test was done by the oral as well as the intravenous routes. In the oral test, 50 to 55 Gm. of dextrose were given orally, while in the intravenous test, one-fifth of the oral dose was administered. The blood glucose was estimated every ½ hour in the case of the oral test and every ¼ hour in the case of the intravenous test. (Figures 2, 3, 4).

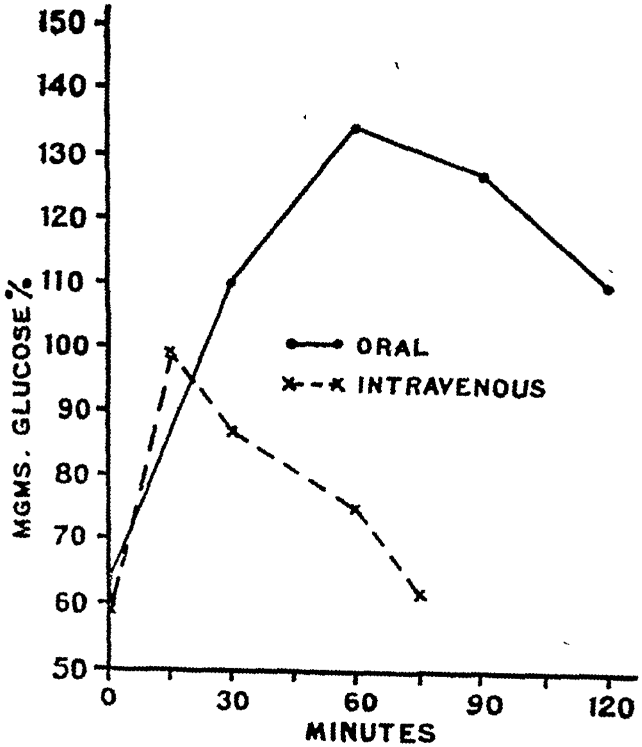

Fig. 2.—Glucose tolerance test (Case 1).

It was seen that the fasting blood sugar level was low in all cases, values as low as 60 mg. being obtained in three cases. Only in one case was the fasting blood sugar level normal. With the oral administration of glucose a slow and steady rise in the blood sugar level was

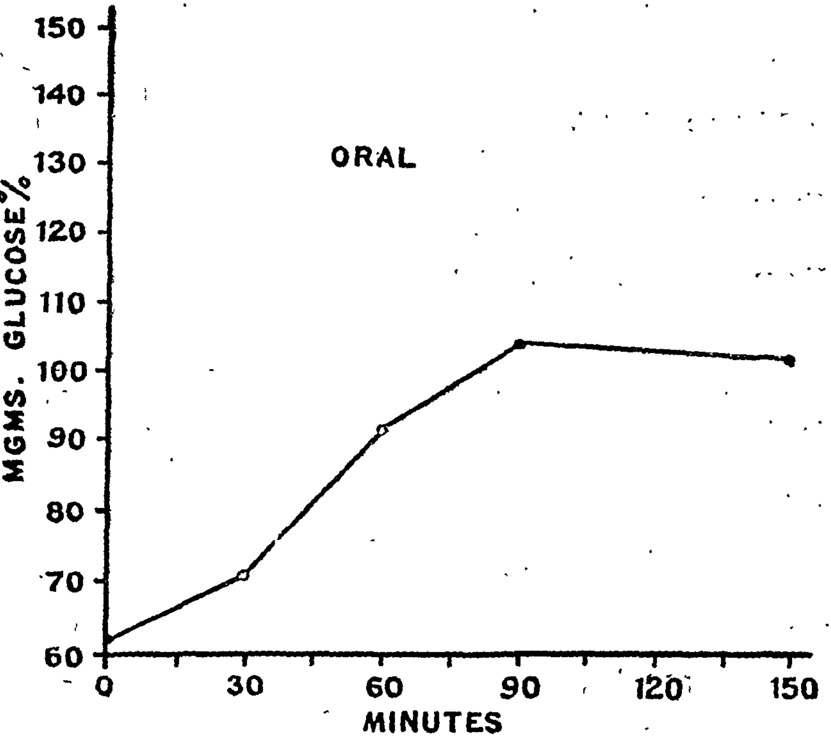

Fig. 3.—Glucose tolerance test (Case 5).

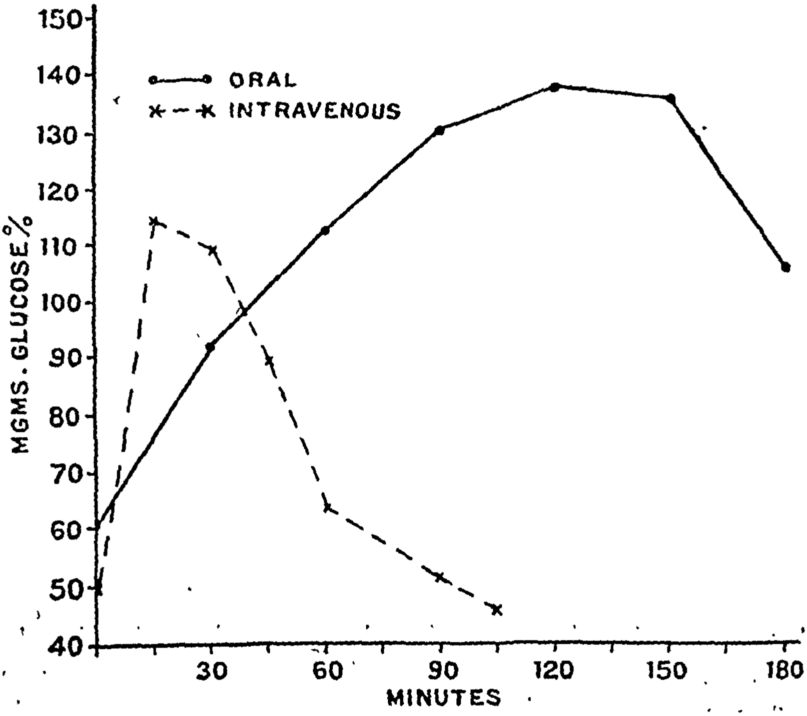

Fig. 4.—Glucose tolerance test (Case 6).

observed. It was noticed in these cases that this rise was maintained even at the end of the second hour. It was not till 2½ hours after the administration of glucose that the blood glucose level began to drop. At the end of three hours, though the blood sugar level had begun to drop, it was still appreciably raised above the fasting level. This continued rise and delayed fall may be indicative of either slow alimentary absorption of glucose or defective utilisation of glucose or of both. In two cases in which the intravenous glucose tolerance test was done in addition to the oral test, no gross abnormality was detected in the intravenous glucose tolerance curves. The low fasting blood sugar levels in these cases, raise the question as to how far the mental changes observed in these cases are the result of hypoglycemia. The abnormal continued rise of blood sugar after glucose administration is, probably, partly to be explained by the lowered rate of alimentary absorption of glucose, which has been known to occur (Chakrabarty[4]). On the other hand, the work of Davies[5] has shown that islets of Langherhans may undergo changes in protein deficiency states, and the question arises, how far these changes, if present, may account for abnormal glucose tolerance curves. It will be seen, later, that examination of the pancreas in five cases of nutritional edema that came to autopsy, revealed that the islet tissue was preserved in all cases and indeed was found to be unusually prominent. Holmes and Trowell[6] have shown that in cases of malignant malnutrition, the liver is unable to store glycogen. The failure of the liver to store glycogen in cases of nutritional edema may also account for the continued abnormal rise of blood sugar giving a pseudo-diabetic response in these subjects. However, in the observation of the two cases in which the intravenous glucose tolerance test was done in addition to the oral test, the intravenous glucose tolerance curve did not reveal gross abnormalities, which may suggest that the abnormal oral glucose tolerance curve is mainly due to delayed alimentary absorption of glucose. It may not, however, be denied that the other mechanisms discussed above may also be involved in some cases. Abnormal types of glucose tolerance curves in nutritional edema have also been reported by other workers (Bose, *et al.*[3]).

PATHOLOGICAL CHANGES

Anemia :—Anemia of varying degrees was found in all the cases investigated. The results of hematological examination of typical cases are given in Table 2 in which the severity of the edema and the anemia in each case are also compared.

The peripheral blood picture was of the macrocytic type in the majority of cases, while only ten cases had the microcytic hypochromic type of anemia. Sternal marrow examination in two of the subjects who showed profound macrocytosis, revealed an early normoblastic

TABLE 2.—*Hematological Values.*

No.	Grade of edema.	R.B.C. million/ cu. mm.	Hb. Gm. per cent.	P.C.V. %	M.C.V. cu. microns.	M.C.H. γγ	M.C.H.C. %	W.B.C. cu. millimeter.	Remarks.
1.	+ + +	3.33	8.9	30	90.9	26.7	29.7	..	
2.	+ + +	4.16	12.1	34	81.7	29.1	35.6	10,750	
3.	+ + +	3.31	10.4	34	103.8	31.4	30.6	14,000	
4.	+ + +	4.78	12.8	39	81.6	21.8	32.1	11,800	
5.	+ +	3.04	10.1	28	92.1	33.2	36.1	4,900	
6.	+ +	2.25	10.5	41	182.2	46.7	25.6	8,400	Sternal marrow done—Early normoblastic reaction.
7.	+ +	1.92	8.6	36	187.5	44.8	23.9	4,000	
8.	+ +	3.95	12.5	41	103.8	31.6	30.5	6,800	
9.	+ +	4.08	12.1	41	100.5	29.7	29.5	3,600	
10.	+ +	3.21	7.2	24	74.8	22.4	30.0	..	
11.	+ +	3.16	8.9	34	107.6	28.2	26.2	..	
12.	+	2.87	12.1	41	142.8	42.1	29.5	13,200	
13.	+	2.86	6.6	25	87.4	23.1	26.4	5,600	

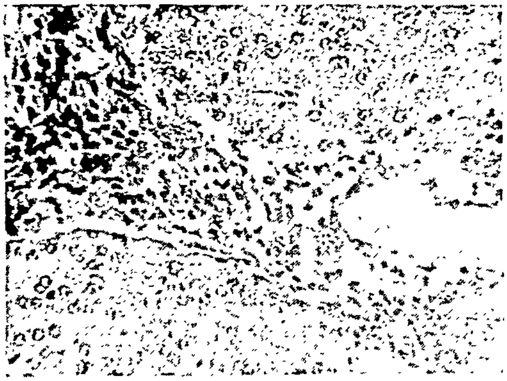

Fig. 5.—Liver x 430. Hematoxylin and Eosin. Clearly showing periportal cellular infiltration.

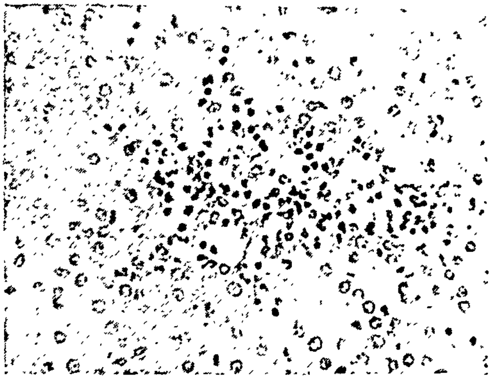

Fig. 6.—Liver x 430. Hematoxylin and Eosin. Showing a patch of necrosis with cellular infiltration.

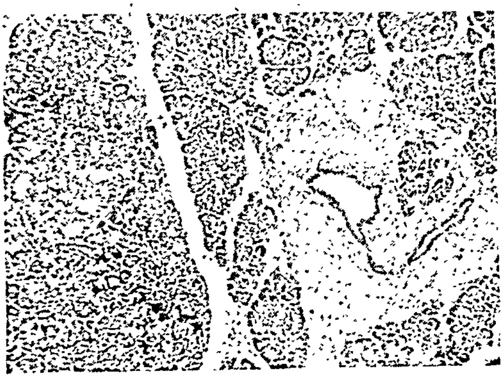

Fig. 7.—Pancreas x 100. Hematoxylin and Eosin. Showing hypertrophy of the islets of Langerhans and severe periductal fibrosis.

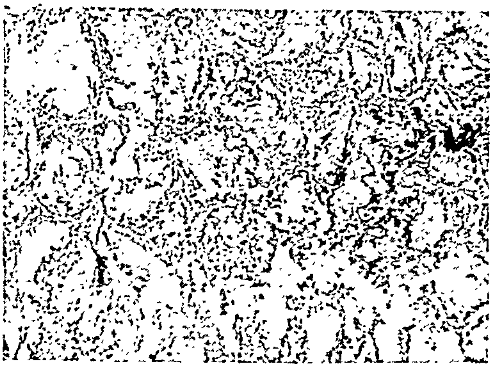

Fig. 8.—Testis x 100. Hematoxylin and Eosin. Showing atrophy of the seminiferous tubules with complete loss of the several layers of cells.

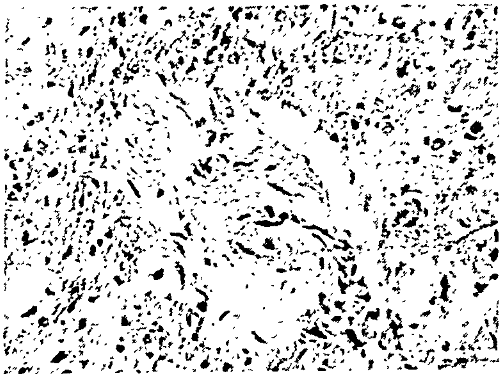

Fig. 9.—Myocardium x 430. Hematoxylin and Eosin. Showing the irregular arrangement of the muscle fibres with loss of cell outline and absence of nuclei.

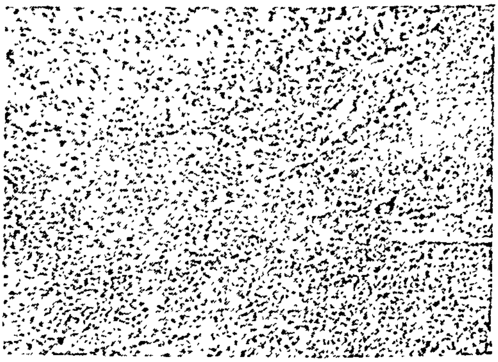

Fig. 10.—Adrenals (Cortex region) x 100. Hematoxylin and Eosin. Showing necrosis and severe hemorrhage.

reaction of the marrow. Evidence of ankylostome infestation was present only in eight cases. It would seem from the foregoing that the predominant type of blood picture in uncomplicated cases of nutritional edema is a normochromic macrocytic type of anemia associated with an early normoblastic bone marrow. This observation is in line with that of other workers (Keys *et al.*[9]). It was found that prolonged and persistent treatment with an adequate diet containing high levels of protein was required to correct anemia in these cases.

In the series reported, five cases expired while under investigation and treatment. Autopsy was carried out only in four of these cases and the striking feature observed in all of them was the considerable diminution of body fat and the severely waterlogged condition of the tissues. Fluid was present in the pleural and peritoneal cavities in all subjects and the intestines and abdominal viscera appeared edematous.

Histological changes described below in the liver and the testes are based on biopsy material besides the post-mortem specimens, while the report of changes in the case of other organs are based on the autopsy materials.* (Figures 5 to 10.)

Liver :—The general architecture of the liver parenchyma was maintained. In almost all the specimens, however, the normal radial pattern of the liver cords was disturbed to a great extent. They were irregular and tortuous and in certain areas their continuity was broken. The liver cells were not found to contain fat, unlike cases of the nutritional edema syndrome in children. Except in one subject, in whom a few cells here and there contained vacuoles with nuclei pushed to the periphery, fatty infiltration was never encountered. On the other hand, evidence of focal necrosis was frequently present. The parenchymal cells were found crowded together at several places with their cell outlines obscured. The nuclei of these cells showed pyknotic changes. Patches of necrosed liver cells, infiltrated with lymphocytes, plasma cells and occasional eosinophils were also found irregularly scattered ; here and there polymorphs were also seen, indicating the activity of the process.

The liver cells were found to show varying grades of staining reaction. Some cells had a brownish red, coarsely granular cytoplasm while in many others the cytoplasm was homogeneously eosinophilic, indicating the presence of hyaline necrosis. There was evidence of the presence of brownish black pigment in several of the cells. The identity of this pigment and its relationship, if any, to the chromolipoid pigment described by Sherlock and Walshe[13] in cases of hunger edema require investigation.

The sinusoids were inconspicuous in those areas where the liver cells were crowded together, while distended at other places. Such distended sinusoids were engorged with red cells in quite a few places. The reticuloendothelial cells lining the sinusoidal spaces were swollen and proliferating, and many of them were found to contain brownish black coarsely granular pigment, which was probably hemosiderin.

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*We are grateful to Professor P. N. Wahi for his report on these specimens,

The central veins showed irregularity of their lumen at some places, while in other areas, the cells surrounding them were undergoing necrotic changes, the wall of the vein only showing a thickening and marked infiltration resulting in the narrowing of their lumen. The portal tracts were prominent and were heavily infiltrated with lymphocytes and plasma cells. In some sections, newly formed bile ducts were also seen.

There was a marked increase in periportal connective tissue in all cases and in places the fibrous tissue bands were seen extending deeper into liver lobules. In some specimens, there was evidence of proliferation of the biliary epithelium in the portal tracts.

To sum up, therefore, the characteristic findings in the liver were (a) absence of fatty infiltration, (b) the presence of focal, patchy necrosis, c) marked connective tissue proliferation in the periportal regions and (d) some pigmentary changes. More detailed investigations on the comparative changes in the liver in these cases and in cases of nutritional edema syndrome in children are in progress.

Pancreas :—The pancreatic acini were found to be normal though bands of fibrous tissue were seen traversing the lobules. The serous cells of the acini were close to each other, and in between them, in a few places, small ducts and ductules were seen. The cytoplasm stained homogeneously at most places, while here and there vacuoles of varying sizes were also present. The nuclei in the majority of the cells were vesicular and showed degenerative changes in the form of fragmentation and pyknosis. The ducts were visible prominently at a few places, while at others, they were considerably narrowed and surrounded by dense bands of fibrous tissue indicating periductal fibrosis.

The islets of Langherhans were prominently seen in all cases examined and were indeed apparently hypertrophied in two cases.

Testes :—The fibrous capsule of the testes—tunica albuginea, was normal and of the adult type. The seminiferous tubules were of varying sizes and shapes, and their lumena were blocked and narrowed at several places due to close approximation of the epithelial cells. The lining cells were frequently found crowding together in the centre. The several layers of epithelial cells like spermatogonia, spermatocytes and spermatids could not be defined, and at most places the number of layers of these cells was very much reduced and no evidence of spermatogenesis, in its various phases, was visible. The nuclei of the lining cells of the tubules did not show any division indicating arrest of function of the tubules. In a few areas in some sections, the cells were actually detached at many places and were lying loose in the lumen. The distinction between the various types of cells was difficult and they were also found to show degenerative changes. Cells of Sertoli, however, were relatively normal with clear cytoplasm and well staining nuclei. In one section, these cells as well as the spermatogonia and spermatocytes were found to contain reddish, crystalline, needle-shaped structures normally reported as seen in Leydig's cells.

The interstitial tissue appeared normal in all cases except one, in which only a very few Leydig's cells were seen.

Heart :—The muscle fibres had lost their cross striations at mos places and were lying close to each other in more or less disorderly fashion. Some cells had lost their outline completely, and in others the cell outlines were hazy at most places and the cytoplasm was finely granular or homogeneous. The staining reaction also varied from place to place. The nuclei were vesicular and pyknotic. At some places the cytoplasm showed fine granules of brown colour.

Adrenals :—The adrenals were examined in two cases. In one of these, the glands showed evidence of severe hemorrhage at autopsy. This case had an acute bout of diarrhea and was unconscious and comatose for some hours preceding death. Histologically, the gland showed complete necrosis, with large numbers of red cells, polymorphs and lymphocytes. The various zones could not be differentiated. Degenerative changes were visible in the cortex, while the medulla was completely necrosed. The possibility that sudden deaths in cases of malnutrition might probably be due to the necrosis of the adrenals seems to deserve investigation.

Small Intestines :—The interglandular substance of the small intestines was infiltrated with lymphocytes and plasma cells. There were no atrophic changes in the glandular portion of the mucous membrane. This finding is contrary to what one would expect in cases of chronic malnutrition where diarrhea is often attributed to atrophy of the mucosa of the small intestine. It is probable that the diarrhea observed in the above cases was not entirely due to structural alterations in the mucous membrane.

Kidneys :—Early cloudy swelling of the tubules and venous congestion of the organ were noticed. The glomerular tufts and the interstitial tissue of the kidney were normal. In the light of these findings, the oliguria in cases of nutritional edema cannot be due to organic changes in the kidney but probably results from functional alterations.

DIAGNOSIS

Cardiac and renal edema can be easily excluded in these cases. The condition may be distinguished from wet beri-beri and epidemic dropsy by the distinctive cardiovascular and other changes and the dietary history. The marked bradycardia, the 'thick' speech, the sparse hair, the mental changes and the subnormal temperature and edema have caused this condition to be mistaken for myxedema. Actually, three of our cases were being treated as myxedema when they were first seen. The nature of the edema and the dietary history should help to avoid this mistake. It is, however, possible that the misleading clinical signs are partly referable to hypothyroidism caused by malnutrition.

PROGNOSIS

The mmediate prognosis of a case of nutritional edema roughly depends on the severity of the edema and the duration for which the edema has lasted. Cases which have had severe edema of Grade II and III for several weeks usually take a much longer period for recovery and are more likely to end fatally, than the subjects with slight edema of recent onset. These considerations, however, are not apparently infallible indices of prognosis. We have had fatalities among cases showing moderate edema of Grade II and satisfactory recoveries among cases with severe edema of Grade III.

The presence of intractable diarrhea decidedly worsens the prognosis. In four out of the five cases that ended fatally, diarrhea was the complication. Chronic infections, like ulcers in the legs, definitely delay the recovery. On the other hand, these infections themselves are relatively resistant to treatment unless the nutritional status is also simultaneously improved.

Mental changes when present interfere with feeding and thus correspondingly worsen prognosis. In fact, the biggest hurdle in the treatment is to get the patient to co-operate in the feeding programme. In our experience, a reliable indication of good prognosis in a case is the ability of the patient to take to the dietary regime on which he is put. However, one of our patients who was able to take to the dietary regime and followed it for several weeks, died suddenly without showing improvement. Evidently, if malnutrition lasts long enough, a stage of irreversibility may be reached. In children with a nutritional edema syndrome, we have also had sudden deaths under similar circumstances.

In this series, five cases ended fatally. Four of these deaths followed on intractable diarrhea resulting in a state of collapse. One patient who was apparently doing well died suddenly. Cases in this series have not been followed for a sufficiently long period to assess the sequelae and ultimate prognosis.

TREATMENT

The edema tends to get worse when the patient is ambulant and to subside in the recumbent posture, probably because of the relative polyuria in the latter position. This effect of posture on the edema has also been observed by other workers (Denz[6]). It is, therefore, advisable to ensure rest in bed during treatment. This, however, is not difficult to enforce considering the marked weakness of the patients.

The temptation to institute an adequate high protein therapy from the very start has to be tempered with the knowledge that an abrupt increase in the intake of food in these patients, not infrequently, precipitates digestive upsets like diarrhea. We have, therefore, followed the practice of working up to the ideal diet gradually. The dangers of too rapid feeding programmes have been pointed out by other workers (Keys[9]). The dietary regime we have followed here is to put the patient on the basic hospital diet, which will supply about 55 Gm. of protein and 2,300 calories per day. In addition, the patient is put on two ounces of dry skimmed milk powder (equivalent to 8 ounces of milk) made into a thick paste on the first day. The advantage of the skimmed milk paste is that it enables a fair amount of protein to be given without much increase in the bulk of the food. The amount of skimmed milk is steadily increased till on the tenth day the patient gets 6 ounces of skimmed milk powder. We have also tried oral casein hydrolysate (ammino-xyl) in the place of skimmed milk with equally good results. The administration of skimmed milk and oral casein hydrolysate, both of which have a peculiar flavour, to these patients with disordered appetites, calls for much persuasive effort. We have not tried intravenous protein hydrolysate therapy or plasma transfusions in these cases. While some extremely advanced cases may benefit by this line of treatment, we believe that a majority of cases can be successfully treated by oral high protein therapy alone.

In children we have gained the impression that the parenteral administration of testosterone propionate was a useful adjuvant to oral high protein therapy. We have not yet tried testosterone propionate in adult subjects. Mercurial diuretics are known to be successful in relieving the edema temporarily but we have avoided resorting to this irrational symptomatic therapy. Where, however, the edema is very severe, diuretics may be used temporarily.

An important consideration in the treatment is to protect the patient from intercurrent complications, during the several weeks required for his full recovery. Diarrhea is a dreaded complication in these cases. If mild, the diarrhea usually responds to high protein therapy and does not require any special measures. In more severe cases, however, it is necessary to employ astringents and antibiotics. Other chronic infections which may inhibit recovery have also to be controlled with antibiotics.

RESULT OF TREATMENT

In cases treated on these lines, the response was satisfactory. In all cases, the improvement was heralded by a marked increase in the urinary output. Cases with a 24 hour urinary output of 250 to 350 cc. before treatment were found to excrete as much as 3 litres within a week after the institution of treatment. With the onset of this diuresis, there was a progressive disappearance of the edema. Edema of Grade II was found to disappear completely in the course of 3 to 4 weeks. In 4 cases where serial plasma protein determinations were carried out, it was noticed that there was no appreciable increase in these values at a time when clinical improvement had set in ; there was no parallelism between the disappearance of clinical edema and the rise in plasma protein values.

The disappearance of clinical edema was, however, no indication of the full rehabilitation of these patients. Even after the edema had cleared up, the patients continued to feel very weak. Apparently, continued feeding, with an adequate diet for several months, is required to restore these patients to normal health.

SUMMARY

Thirty-nine cases of nutritional edema have been investigated. The clinical features of these cases have been described in detail.

Observations have been made regarding the levels of serum protein fractions, serum sodium and chloride, and the glucose tolerance in some of them. The significance of these biochemical observations has been discussed.

Histological changes in the various organs from specimens obtained at biopsies and autopsies have been described.

The treatment adopted has been outlined and the response to treatment discussed.

ACKNOWLEDGMENT

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ORIGINAL ARTICLE

A NEW METHOD FOR THE DETECTION OF LEPROSY BACILLI IN NEURAL CASES AND CONTACTS

N. Figueredo * and S. D. Desai *

While the detection of lepra bacilli in the skin of lepromatous patients presents no difficulty, the finding of even a few bacilli in neural cases has taxed the patience of workers for many years.

The method described by us[2], and followed for over ten years, resulted in only 39 per cent of neural cases being positive for a few bacilli on the first examination and 43 per cent positive on subsequent examinations carried out during an average period of 3 years in individual cases.

The preparation of smears for the detection of bacilli in contacts described by us[1] was easy, but the prolonged search needed for the demonstration of a few bacilli made this method unsatisfactory for the routine examination of such individuals.

Ever on the search, therefore, for a method which would reveal a larger number of bacilli both in neural cases and in contacts, various methods were tried and rejected till the probability of obtaining appreciable numbers of bacilli from a piece of skin by extraction with chloroform, the method used in the preparation of partly defatted lepromin, struck us as being likely to give the desired results.

The following is a description of the methods tried and the results obtained in leprosy cases and their contacts.

METHODS FOR THE DETECTION OF LEPROSY BACILLI

Taking the Biopsy :—The skin, after being wiped with a 5 per cent carbolic lotion, is pinched between the blades of a forceps, and an incision is made with a sharp scalpel deep into the corium. Another incision, about 3 mm. apart, is made at an angle of 25° to the first so as to meet the base of the first incision in the corium, and the wedge-shaped piece of skin is removed. For a comparison of the results by different methods a larger piece of skin was removed and divided into equal parts.

Extraction of Bacilli :—

Method I.—The piece of skin is placed on a slide and is immediately pressed flat with the blade of the scalpel and with a rotary motion a smear is made. The flattened tissue is then rejected. The smear is fixed by heating very gently over a Bunsen burner. This is the routine method adopted in the Acworth Leprosy Home.

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* From the Acworth Leprosy Home, Matunga, Bombay.

Method II.—The same process is adopted as in method I, except that 4 to 6 drops of chloroform, containing 2.5 per cent acetone, are dropped on the tissue before subjecting it to pressure with the blade of the scalpel.

Method III.—The piece of skin is placed in a centrifuge tube containing 2.5 cc. of chloroform (with 2.5% acetone) and allowed to soak for 4 to 5 hours. With a glass rod, the tissue is pressed against the sides of the tube with a rotary motion under the surface of the chloroform till the piece is flattened. The tissue is then rejected. The chloroform in the tube is evaporated over a water bath till a few drops remain. When cool, about 5 cc. of sulphuric ether are added and centrifugalised at 3,000 r.p.m. for 15 minutes. The ether is then decanted, leaving a few drops at the bottom of the tube. These drops are stirred with a platinum loop and poured, drop by drop, from the tube on a slide warmed previously over the flame of a spirit lamp, and a smear is made. A few drops of ether are added to the tube to wash out the residue and these drops are added, drop by drop, to the smear. The residue in the tube is washed out a second time with a few drops of ether, which are added, drop by drop, to the smear.

Fixation :—The smear is fixed by gently warming the slide over the flame of a spirit lamp or with the aid of Carnoy's fluid[3]. The slide, with the smear downwards, is placed in contact with the Carnoy's fluid which is poured in a staining dish, and kept for 10 minutes. The smear is then dried in an incubator at 40° C or by gently warming over a spirit lamp.

Staining :—Ziehl-Neelsen's method is adopted for method I.

For method II, the carbol-fuchsin is allowed to flood the slide for 25 minutes without heating at any time. The decolourising is done with 10 per cent hydrochloric acid in distilled water, without alcohol or rectified spirit. Counterstaining is done by methylene blue (5 drops of a 1% solution in 20 cc. of distilled water).

For method III, the carbol-fuchsin is allowed to flood the slide and is kept for 10 to 15 minutes without heating. If Carnoy's fluid is used as a fixative, the carbol-fuchsin is heated until vapour is seen rising. When the vapour subsides, the heating is repeated and the stain is allowed to remain for 5 minutes. Decolourisation is done with 10 per cent hydrochloric acid in distilled water without alcohol or rectified spirit. Counterstaining is done with 1 per cent methylene blue in distilled water.

COMMENTS

In a few neural cases, bacilli could be satisfactorily demonstrated by the chloroform extraction method (method III) when the routine method gave negative results. In neural cases, positive for bacilli by the routine method, a larger number of bacilli were found by method III.

TABLE 1.—*Results of Examination of Neural Cases by the Three Methods.*—

Serial No.	Type and classification of leprosy.	Description of the lesion examined.	Number of bacilli found by		
			Method I.	Method II.	Method III.
1	Nt1	Well-defined red, raised hard anesthetic macule.	N	N	33
2	Nt1	,,	2	6	30
3	Nt2	,,	N	N	100
4	Nt2	,,	N	N	18
5	Nt2	,,	N	N	28
6	Nt2		1	5	30
7	Nt2	,,	N	N	33
8	Nt2	,,	N	4	46
9	Nt2	,,	N	N	36
10	Nt2	,,	N	6	56
11	Nt2	,,	N	5	3 to 4 in each field.
12	N3t	,,	9	15	90
13	Nt2	Well-defined red, raised slightly soft anesthetic macule.	12	25	4 in each field.
14	Nt2	,,	1 in each field	2 to 3 in each field.	15 to 20 in each field.
15	Nt2	,,	4 to 5 in each field.	10 to 12 in each field.	50 to 60 in each field.
16	Na2t2	Well-defined red, raised slightly soft anesthetic macule.	N	N	5 to 10 in each field.
17	Na2t2	,,	10	25	3 to 4 in each field.
18	N3t	,,	5	20	150
19	Nt1	Hypopigmented raised anesthetic macule.	N	3	40
20	Nt1	,,	N	N	45
21	Nt2	,,	N	2	30
22	Nt2	,,	N	N	30
23	Nt2	,,	N	N	33
24	Ns1	Hypopigmented flat anesthetic macule.	N	N	30
25	Ns1	,,	N	N	30
26	Ns1	,,	N	N	39
27	Ns1	,,	N	N	40
28	Ns1	,,	N	N	36
29	Ns1	,,	N	4	44
30	Ns1	,,	N	N	18

TABLE 1.—(*Contd.*)

Serial No.	Type and classification of leprosy.	Description of the lesion examined.	Nnmber of bacilli found by		
			Method I.	Method II.	Method III.
31	Ns1	Hypopigmented flat anesthetic macule	N	N	12
32	Ns2	,,	N	4	30
33	Ns2	,,	N	5	40
34	Ns2	,,	N	N	33
35	Ns2	,,	N	N	18
36	Ns2	,,	N	N	30
37	N3s	,,	N	N	34
38	N3s	,,	N	N	30
39	N3s	,,	N	N	24
40	N3s	,,	2	4	104
41	N3s	,,	N	7	42
42	Ns1	Hypopigmented macule with anesthetic dark centre.	N	N	12
43	Na2s2	,,	6	10	90
44	Na1	Non-visible anesthetic area (acroteric).	N	N	50
45	Na1	,,	N	4	36
46	Na3	,,	N	N	18

TABLE 2.—*Results of Examination of "Doubtful" Cases by the Three Methods.*

Serial No.	Age.	Description of the lesion examined.	Number of bacilli found by		
			Method I	Method II	Method III
1	4 months	Small hypopigmented flat macule.	N	N	30
2	,,	,,	N	N	5
3	2 years.	,,	N	N	15
4	3 ,,	,,	N	2	20
5	3 ,,	Small hypopigmented flat macule.	N	2	10
6	4 ,,	Small hypopigmented flat macule without sensory changes.	N	N	14
7	6 ,,	Small hypopigmented papule without sensory changes.	N	N	1 to 2 in each field.
8	16 ,,	Red and raised area without sensory changes.	N	N	30

TABLE 3.—*Results of Examination of Contacts Without Lesions by Method III.*

Serial No.	Age in years.	No. of bacilli found.	Lepromin reaction.	
			Early in mm.	Late in mm.
1	1	16	N.O.	N.O.
2	1½	N	N	N.O.
3	2	N	N	N.O.
4	2½	20	10	3
5	3	N	N	N.O.
6	4	N	N	N.O.
7	5	20	10	3
8	6	25	N	N
9	7	60	N.O.	5
10	7	31	12	N.O.
11	7	22	N.O.	N.O.
12	7	N	N.O.	N.O.
13	8	20	N.O.	3
14	8	N	N	N
15	8	N	N	N
16	9	30	N	N
17	9	N	N	N
18	9	N	N	N
19	10	26	10	5
20	11	20	N	N
21	11	20	10	5
22	11	9	5	N.O.
23	12	16	N.O.	N.O.
24	12	9	20	5
25	15	15	N.O.	N.O.
26	17	N	N	N
27	17	6	15	N.O.
28	19	N	N	N
29	20	50	17	N.O.
30	21	18	10	5
31	22	15	N.O.	5
32	22	16	N.O.	10
33	22	N	N.O.	N.O.
34	22	20	N.O.	N.O.
35	25	28	Not done.	..
36	25	24	10	5
37	26	18	10	4
38	28	N	N	N
39	28	15	8	5
40	29	13	N.O.	N.O.
41	30	15	10	5
42	30	N	N.O.	N.O.

TABLE 3.—*Results of Examination of Contacts Without Lesions by Method III.*

Serial No.	Age in years.	No. of bacilli found.	Lepromin reaction.	
			Early in mm.	Late in mm.
43	30	N	N	N
44	30	15	7	5
45	33	N	N	N
46	35	18	10	5
47	35	N	N	N
48	40	15	10	N.O.

N= Negative. N. O.=Not observed.

In 8 doubtful cases the diagnosis could be arrived at definitely, by the demonstration of bacilli by method III.

Results of the examination of contacts by method III confirmed our previous findings[1], obtained by the routine method of smear examination, and the bacilli could be easily demonstrated.

Method III therefore should have wide application in the following situations :—

(1) Examination of negative or arrested neural cases.

(2) Doubtful cases.

(3) Contacts without lesions.

(4) Sulphone-treated cases, negative for bacilli by ordinary methods of examination.

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ORIGINAL ARTICLE

A PRELIMINARY TRIAL OF AUREOMYCIN IN THE TREATMENT OF TROPICAL EOSINOPHILIA

C. K. Prasada Rao * and P. Krishnan †

During our work on tropical eosinophilia, we came across a few cases where arsenic was contra-indicated for some reason or other. Up to now, there has been no alternative treatment for tropical eosinophilia, except arsenic, in some form or other. It was decided to try the effect of aureomycin as there is a growing belief that tropical eosinophilia is due to a virus infection of the lungs, and this drug has been shown to be effective in other viral infections of the lung, namely influenza and virus pneumonia.

Five cases were treated with aureomycin, and abstracts from the records of four cases, treated with arsenic, are also given for comparison.

CASE REPORTS.

Case 1. S. A., a male aged 26 years, occupied as a clerk, started complaining, *6 months ago, of an irregular fever, cough with slight expectoration.* Later, he developed wheezing which was worse at night. A few rales and rhonchi heard diffusely all over both lungs. The blood count before treatment was : total white blood cells, 16,200 ; polymorphonuclears 24 per cent ; lymphocytes. 13 per cent ; eosinophils, 61 per cent ; monocytes, 2 per cent.

Treatment consisted of one capsule of aureomycin every three hours. After 13 capsules had been administered, the patient developed nausea and loose stools. After giving 21 capsules, the nausea and loose stools became much worse and the administration of the drug had to be stopped after 29 capsules. The total dose was 7.25 Gm. in 4 days.

After the completion of the treatment the physical findings in the chest had disappeared and the patient said that he felt better.

The blood count after completion of the treament was as follows :—White blood cells, 16,000 ; polymorphonuclears, 41 per cent ; lymphocytes, 30 per cent ; eosinophils. 29 per cent.

Case 2. A, a male aged 30 years, and a merchant by occupation, came with a cough that started insidiously 2 months ago and later wheezing developed. On the day of examination, there were no physical findings in the chest. The blood count before treatment was : Total white blood cells, 42,000 ; polymorphonuclears, 22 per cent ; eosinophils, 54 per cent ; lymphocytes, 22 per cent ; monocytes, 2 per cent. One capsule of aureomycin was given every three hours up to a total of 24 capsules, *i. e.*, 6 Gm. in 4 days when the drug had to be discontinued as the patient developed severe nausea and vomiting. However, the patient reported that he felt better. The count after treatment was : white blood cells, 16,000 ; polymorphonuclears, 22 per cent ; eosinophils, 68 per cent ; lymphocytes. 10 per cent.

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Case 3. R., a student aged 25 years, complained of a cough that started insidiously with expectoration, three months ago. Both persisted with slight ups and downs ever since. The blood count before treatment was : white blood cells, 17,400 ; polymorphonuclears, 30 per cent ; lymphocytes, 20 per cent; eosinophils, 50 per cent. One capsule of aureomycin was given every four hours for five days. (Total of 28 capsules, *i.e.*, 7 Gm. in 5 days.) There were no physical findings. The count after treatment was : white blood cells, 12,400 ; polymorphonuclears, 50 per cent ; lymphocytes, 26 per cent ; eosinophils, 22 per cent ; morphonuclears, 2 per cent. Subjectively, the patient felt better.

Case 4. Vi., a female medical student aged 21 years. complained of a cough and wheezing of insidious onset, of a few months duration. There were no physical findings. The count before treatment was : white blood cells. 21,500 ; polymorphonuclears, 30 per cent ; lymphocytes, 20 per cent ; eosinophils 50 per cent. One capsule of aureomycin was given every six hours to a total of 25 capsules (6.25 Gm. in 6 days). The white cell count after treatment was 12,600 ; eosinophils, 16 per cent. The patient was relieved of her symptoms.

Case 5. Va., a female medical student aged 24 years had been having a cough with expectoration and wheezing ever since childhood; it was diagnosed as chronic bronchitis and was treated as such without any permanent benefit. About six years ago, her condition was recognised to be tropical eosinophilia and she was given three courses of arsenic spread over a period of four years. After each course there was a remission which was not sustained for more than a year. Hence, it was decided to try the effect of aureomycin. On the day of examination there were no physical findings in the lungs. The count before treatment was : total white blood cells, 14,500 ; polymorphonuclears, 36 per cent ; lymphocytes, 12 per cent ; monocytes, 1 per cent ; eosinophils, 51 per cent. She was given a total of 30 capsules of aureomycin. one capsule every six hours (7.5 Gm. in 8 days). The count after treatment was : total white blood cells 11,000 ; eosinophils, 15 per cent. The patient felt relieved. The blood count was repeated after a week and the eosinophils had risen to 35 per cent. The total count was not done and symptoms tended to return.

REPORT OF CASES TREATED WITH ARSENIC

Case 6. T., a male salesman aged 21, complained of wheezing with much expectoration for 2 months. Rales and rhonchi were heard over both lungs. The blood count before treatment was 18,600 ; polymorphonuclears, 40 per cent ; lymphocytes, 10 per cent ; eosinophils, 50 per cent. The patient was given 6 injections of acetylarsan, one every six days. After treatment there were no physical findings in the chest. The count after treatment was : total white blood cells 6,000 ; polymorphonuclears, 57 per cent : lymphocytes. 35 per cent ; eosinophils, 5 per cent ; monocytes, 3 per cent. A month later, there was a return of symptoms, but no count was done.

Case 7. R. L., a male aged 34 years, complained of a cough and wheezing for one month. He had had a similar complaint four years ago.

A practitioner gave him four injections of 'mapharside'. There was a dramatic relief of symptoms. Rales and rhonchi were heard over both lungs. The count before treatment was : total white blood cells, 9,800 ; polymorphonuclears, 35 per cent ; lymphocytes, 15 per cent ; eosinophils, 50 per cent. One injection of 'acetylarsan' was given every six days (a total of 6 injections). The patient was considerably relieved of his symptoms when seen two weeks after completion of the treatment. No physical signs were found in the chest. The count after treatment was : total white blood cells, 5,000 ; polymorphonuclears, 51 per cent : lymphocytes, 40 per cent ; eosinophils, 9 per cent.

Case 8. C., a male aged 24 years, had a cough, wheezing and expectoration for four years. A diagnosis of asthma was made and he was treated on conservative lines with no improvement. No findings in the chest were present on the day of examination. The count before treatment was : white blood cells, 13,000 ; polymorphonuclears, 31 per cent ; lymphocytes, 20 per cent ; eosinophils, 49 per cent. One acetylarsan injection was given every 6 days. (Total of 6 injections).

Condition after treatment : The condition became much worse after the 6th injection and the patient had to be admitted as an in-patient. Rales and rhonchi were heard extensively. The count after treatment was : white blood cells, 10,400 ; polymorphonuclears, 38 per cent ; lymphocytes, 37 per cent ; eosinophils, 22 per cent ; monocytes, 3 per cent.

Case 9. K. V. C., aged 32 years, a male, had wheezing and cough for the last fifteen years.

During summer he was practically free from symptoms, but the condition became worse during the monsoons. Both lungs were filled with rales and rhonchi. The count before treatment was : white blood cells, 25,000 ; polymorphonuclears, 9 per cent ; lymphocytes, 13 per cent ; eosinophils, 78 per cent.

One injection of acetylarsan was given every 6 days. (Total of 6 injections).

The patient felt considerably relieved. A few moist rales and rhonchi were heard over both the lungs. The count after treatment was 10.400 ; polymorphonculears, 36 per cent ; lymphocytes, 30 per cent ; eosinophils, 32 per cent ; morphonuclears, 2 per cent.

TABLE 1.—*Cases Treated With Aureomycin.*

Case No.	Total Dose of Aureomycin in Gm.	Initial Absolute Eos. Count (before treatment).	Final Absolute Eos. Count (after completion of the course).	Initial clinical findings.	Final clinical findings.	Response.
1.	7.25	9,882	4,800	Rales & Rhonchi.	Nil.	+
2.	6	22,680	10,880	Nil.	Nil.	+
3.	7	8,700	2,728	Nil.	Nil.	+
4.	6.25	10,750	2,016	Nil.	Nil.	+
5.	7.5	7,395	1,650	Nil	Nil	+
		Cases Treated with Acetylarsan.				
	No. of injections.					
6.	6.	9,300	300	Rales & Rhonchi.	Nil	++
7.	6.	4,900	450	do.	Nil	++
8.	6.	6,370	2,288	Nil	Rales & Rhonchi.	?
9.	6.	19,500	3,328	Rales & Rhonchi	Rales & Rhonchi considerably less.	+

DISCUSSION

The small series of 5 cases treated with aureomycin does not permit a final conclusion about its efficacy in tropical eosinophilia. A well controlled trial, with untreated cases and cases treated with arsenic as controls, is required before final conclusions can be drawn. The response in the five cases reported warrants further trial.

Of the 5 cases treated with aureomycin, all have shown definite clinical and some hematological evidence of amelioration. None could be considered cured as the eosinophil counts continued to be abnormal. The cases have to be followed further to see whether the eosinophil counts will fall. In one case—Case No. 2—it showed a tendency to rise and there was a tendency for the symptoms to return.

Of the 4 cases treated with acetylarsan, 2 had complete hematological remission and in 2, the eosinophil count decreased considerably. Clinically, 2 of the 4 cases had a complete remission and were free from all signs and symptoms. One case became considerably worse and one had considerable amelioration of symptoms. Increase in the signs and symptoms in tropical eosinophilia after arsenic has been noted by many workers ; but the exacerbation does not last long. This case is unusual, in that the increase in signs and symptoms did not show a tendency to ameliorate as the treatment continued.

The results as tabulated tend to show that the effects of arsenic treatment are more significant. Yet, a definite conclusion cannot be drawn in view of the difference in the time factor in the 2 series. The hematological review in cases treated with aureomycin was done a week after completion of treatment while in the arsenic treated cases it was done after a few weeks. While no definite conclusion can be drawn, the clinical impression is, that aureomycin brings about amelioration of clinical symptoms in a shorter time.

It is proposed to try the effect of aureomycin on more cases of tropical eosinophilia. The results will be communicated in due course.

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ORIGINAL ARTICLE

SINGLE DOSES OF CAMOQUIN IN THE TREATMENT OF MALARIA

M. Y. Ansari *

Drug therapy of malarial infection more or less remains in the same state though much knowledge has been gained regarding the life cycle of the malarial parasite. It has been shown (Shortt *et al.*[6],[7]) that the malarial parasites (*P. vivax* ; *P. falciparum*) pass a pre-erythrocytic stage in the parenchymal cells of the liver in man. These tissue forms or exo-erythrocytic forms which are not acted on by the usual anti-malarial drugs are considered to be the cause of relapses.

Camoquin, one of the new anti-malarial drugs of the quinoline series, like mepacrine, is slowly excreted, thereby remaining in an effective concentration in the blood for over a long period. Simeons and Chhatre[8], keeping in view this property of the drug, were the first to use camoquin in single doses in the treatment of malaria. Later Antonio Ejecito and Merced Duque[1], Chaudhuri and Chakravarty[2], Chaudhuri, Rai Chaudhuri, Ghosh, and Dutta[4] have reported satisfactory results with single doses of camoquin in the treatment of malaria.

In the work reported here single doses of camoquin were employed and the effects of the drug on the temperature, parasitemia, splenic enlargement and the occurrence of relapses were noted. The duration of observation in some cases extended to over 3 years.

METHODS

Of the total number of 28 cases reported here, 24 were treated as in-patients in the Osmania General Hospital, from June 1948 to December 1950 ; the remaining four were treated as out-patients. The duration of stay in the hospital was from a few days to about a month. Some of the hospital cases, after their discharge, reported from time to time for over 3 years (Table 1).

Camoquin, supplied in 1948 in the form of tablets each weighing 0.05 Gm., was administered by mouth in a single dose. The dose varied from 7.33 mg./Kg. body-weight to 10.53 mg./Kg. (Table 1).

No other anti-malarial drug was given prior to or after camoquin to any case except to case number 23, (Table 1) who did not show any response for three days and therefore was given quinine intramuscularly on the 4th day by his family physician. (Table 1, case 23). The blood was examined for the presence of malarial parasites before the

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TABLE 1.—*The Effects of Single Doses of Camoquin in 28 Cases of Malaria.*

Case No.	Type of	Time for temperature to reach normal after camoquin in hours.	Time of disappearance of parasites in days.	Observation period.	Single dose mg/Kg.	Relapse period after camoquin.	Remarks.
1.	B.T.	44	2	18 days	10.23	..	..
2.	B.T.	24	1	3 years 5 months	10.0	8 & 1/2 months	No further relapse after camoquin so far (2 years 8 & 1/2 months.)
3.	M.T.	20	2	5 days	9.04	..	..
4.	B.T. & M.T.	No rise	..	1 day	9.82	..	..
5.	B.T.	No rise	1	12 days	10.47	..	..
6.	B.T.	No rise	1	4 months 8 days	9.67	..	..
7.	M.T.	36	2	6 days	9.64	..	..
8.	M.T.	48	2	10 days	10.18	..	..
9.	B.T.	24	1	6 days	9.9	..	..
10.	B.T.	16	1	3 years 4 months	10.1	..	..
11.	M.T.	36	..	5 days	10.4	..	..
12.	M.T.	44	2	1 month 4 days	10.1	..	Camoquin during fever.
13.	B.T.	34	1	2 years 6 & 1/2 months	9.7	7 months 4 days	No further relapse after camoquin so far. (1 year, 11 months)
14.	B.T. & M.T.	24	1	13 days	10.1	..	Camoquin during fever.
15.	B.T.	24	1	2 years 6 & 1/2 months	9.16	1 month 9 days	Camoquin second time effective no further relapse so far (2 year 6 months)
16.	M.T.	20	1	5 days	10.06	..	..
17.	B.T.	36	3	10 days	10.0	..	..

Table 1. Contd.—*The Effects of Single Doses of Camoquin in 28 Cases of Malaria.*

Case No.	Type of	Time for temperature to reach normal after camoquin in hours.	Time of disappearance of parasites in days.	Observation period.	Single dose mg/Kg.	Relapse period after camoquin.	Remarks.
18.	M.T.	16	2	6 days	9.87	..	..
19.	B.T.	24	1	7 days	9.8	..	..
20.	M.T.	36	2	12 days	10.31	..	..
21.	B.T.	16	2	3 days	9.87	..	..
22.	B.T.	No rise	1	1 year 7 & 1/2 months	7.33	..	..
23.	B.T.	Temperature did not come down to normal for three days.	..	..	9.3	..	Quinine was given on the fourth day (see the text).
24.	B.T.	36	..	9 days	9.5	..	..
25.	B.T.	36	2	1 year 4 months	10.35	..	..
26.	M.T.	16	..	2 days	9.62	..	Camoquin during fever.
27.	M.T.	48	3	18 days	10.53	..	..
28.	B.T.	No rise	..	9 days	9.7	..	..

B. T.—Benign Tertian.
M. T.—Malignant Tertian.

TABLE 2.—*Relation Between Single Dosages of Camoquin and the Relapse Rate.*

Dose mg./Kg. ..	(7.3)	(9.0—9.6)	(9.6—9.8)	(9.8—10.0)	(10.0—10.53)	Total
Number of cases	1	4	6	6	11	28
Number of relapses	0	1 (B.T.)	1 (B.T.)	1 (B.T.)	0	3

B. T.—Benign Tertian.

administration of camoquin. The blood was examined daily after camoquin till it was found to be negative for the asexual forms of the malarial parasite. In all the three cases of relapses reported here, camoquin was administered in the same single does as before and was found to be effective. None of these cases relapsed for the second time.

RESULTS

Total number of cases............28

Sex.

Male 19

Female 9

Age.

Age in years ..	.. (1-10)	(10-20)	(20-30)	(30-40)	(40-50)	(50-60)	Total.
Number of cases	.. 1	4	19	3	..	1	28

Type of infection	.. *P. vivax*	*P. falciparum*	*P. vivax* *P. falciparum*	Total.
Number of cases	.. 16	10	2	28

Effect on Temperature :—The time taken for the temperature to come down to normal after camoquin varied from 16 hours to 48 hours, the average being 29.9 hours (see Table I). In one case of benign tertian infection, (Table I, case No. 23) however, camoquin failed to bring down the temperature for three days. This indicates the possibility of camoquin either being slow in action or ineffective in certain cases of malaria. The cases of malaria treated with single doses of camoquin may be classified into three groups according to the behaviour of temperature after the administration of the drug.

Group 1 :—These cases did not show any rise of temperature after camoquin when it was given in the apyrexial period (see Fig. 1). Five such cases were noted (see Table 1, case numbers 4, 5, 6, 22 and 28). The blood of three of these cases, examined on the day of administration of the drug, was positive for malarial parasites. The cases in the above group are similar to those described by Hamilton[5] and Chaudhuri *et al.*[4] in whom parasitemia was present without any fever.

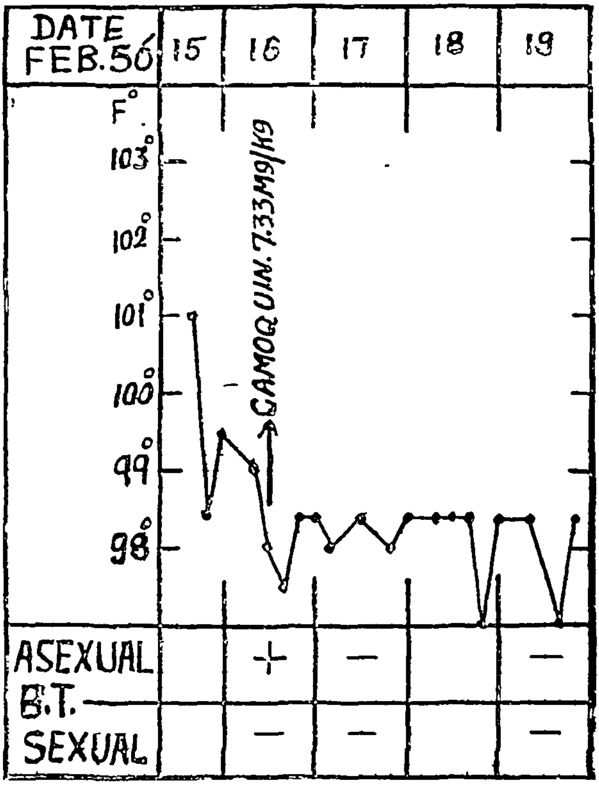

Fig. 1.

Temperature chart showing no rise of temperature following camoquin administration. (Table 1, case number 22) Blood positive for asexual forms of B. T. (Benign Tertian) on the day of camoquin administration.

+ Peripheral blood positive for malarial parasites.

— Peripheral blood negative for malarial parasites.

Group 2.—These cases had a rise of temperature of a lower grade only once following the administration of camoquin in the apyrexial period of the disease. In Fig. 2 and Fig. 3 are shown the effects of camoquin on the temperature in a case of *P. falciparum* and *P. vivax* infection, respectively Most of the cases were found to belong to this group.

Group 3.—In these cases the temperature came down gradually to normal, not to rise again, when camoquin was given during the fever (see Fig. 4). All three cases (Table I, case No. 12, 14, and 27) of this group had *P. falciparum* infection ; case number 14 had *P. vivax* infection as well. This type of effect on the temperature chart has also been observed by Simeons and Chhatre.[8]

Effect on Parasitemia :—The time taken for the disappearance of the asexual forms of parasites from the peripheral blood varied from 1 to 3 days. (See Table I). In cases of *P. falciparum* infection the crescents were not affected and could be seen on the fifth day of treatment.

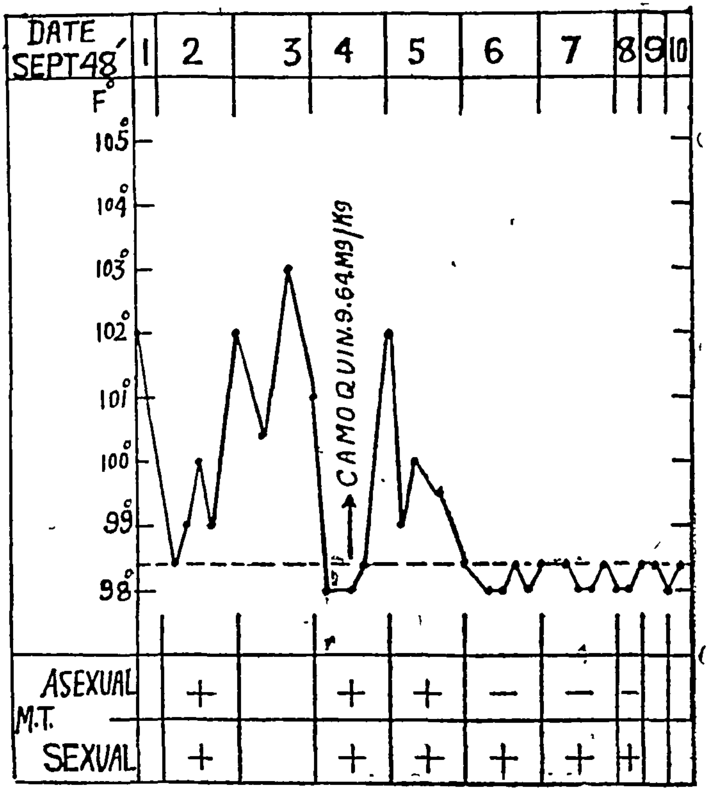

Fig. 2.

Temperature chart showing a rise of temperature of lower grade after camoquin administration in the apyrexial period in a case of M.T. (Malignant Tertian) infection (Table I, case number 7).

+ Peripheral blood positive for malarial parasites.
— Peripheral blood negative for malarial parasites.

Relapses :—During the observation period which extended in some cases to over 3 years (Table I), there were three cases of relapses, all of *P. vivax* infection.

The relapses occurred 8½ months, 7 months and 4 days, and one month and 9 days after treatment with camoquin. The blood of these cases was positive for *P. vivax* during the relapse. Camoquin in the same single dose was given again to these cases and was found to be effective. No relapses were noted in these cases up to the time of writing this paper. (See Table I). Chaudhuri and Chakravarty[2] compared the effects of camoquin in single doses with repeated doses, and found that the relapses were more frequent when the latter method was used. Simeons and Chhatre[8] found that the occurrence of relapses diminished with the increase in the single doses of camoquin. In their observation period of three months, they did not have any relapse in cases which were given single doses of 10 mg./Kg. body weight. The relation between

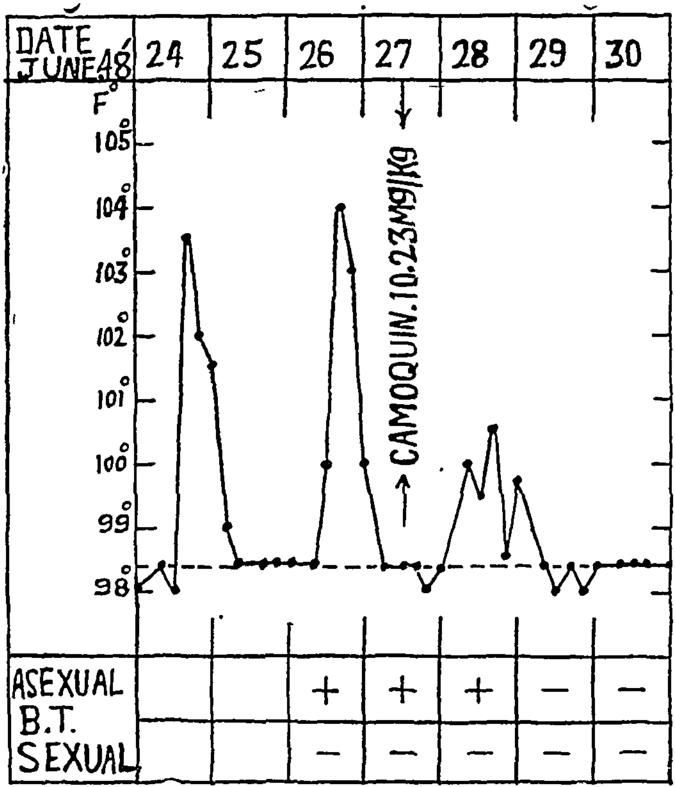

Fig. 3.

Temperature chart showing a rise of temperature of lower grade after camoquin administration in the apyrexial period in a case of B. T. (Benign Tertian) infection. (Table 1 case number 1).

+ Peripheral blood positive for malarial parasites.
— Peripheral blood negative for malarial parasites.

single doses of camoquin and the relapse rate is also noted in this work (see Table 2). This shows that the relapses occurred only when the dosage was below 10 mg./Kg.

Previous Attacks :—Eight cases gave a history of previous attacks of malaria occurring from two months to three years prior to the present illness.

Splenic Enlargement :—The spleen was found enlarged in 20 cases out of the 25 examined. In some cases the spleen was either reduced in size or become impalpable with the treatment.

Blood Report :—All the cases were suffering from some degree of hypochromic microcytic anemia. The differential leucocytic count in the majority of cases showed an increase in the large mononuclear cells. (4%—12%).

Toxic Symptoms :—No toxic symptoms were seen with the dosages used in these investigations.

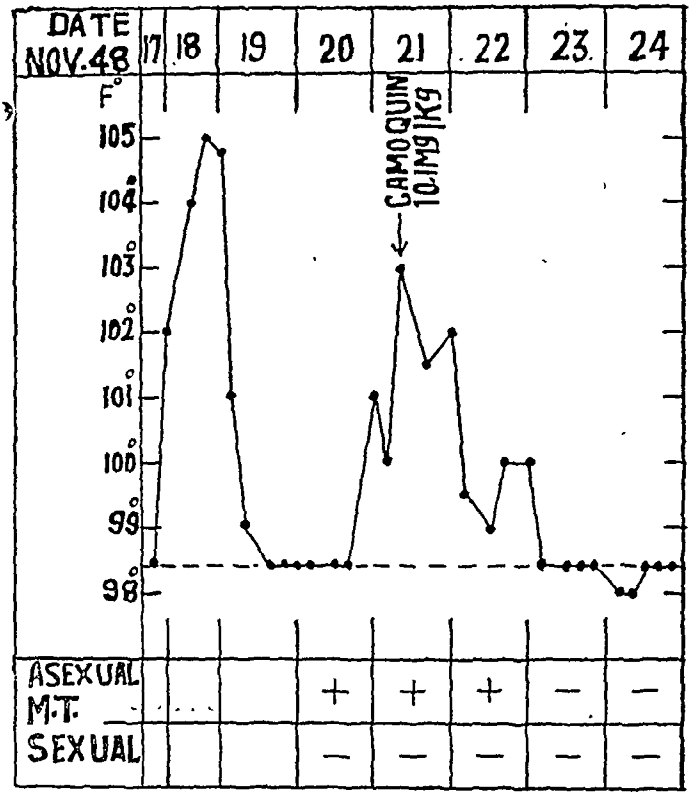

Fig. 4.

Temperature chart showing a gradual fall of temperature to normal when camoquin was administered during the fever in a case of M. T. (Malignant Tertian) Infection. (Table 1 case number 12)

+ Peripheral blood positive for malarial parasites.
— Peripheral blood negative for malarial parasites.

CONCLUSIONS

The results obtained with the single dosage of camoquin in the treatment of malaria show that it is an effective and a safe drug. As compared to the other anti-malarial drugs, like paludrine, it is more rapid in action and it does not produce drug resistance as is found with the use of paludrine[3] (Chaudhuri and Rai Chaudhuri[4]). Camoquin, besides, has also been shown to produce a greater reduction in the relapse rate, as compared to paludrine[4]. Camoquin therefore appears to be a more effective drug than paludrine though more expensive than the latter. The only other drug which is as effective as camoquin, is chloroquin, another derivative of quinoline. The effective single dosages of camoquin (see Table 2), which are likely to reduce the frequency of relapses, lie between 10 mg./Kg. and 11 mg./Kg. of body weight. In an average adult weighing 60 Kg. this will be about 0.6 Gm.

SUMMARY

1. Camoquin in single doses ranging from 7.3 mg./Kg. to 10.53 mg./Kg. was administered in 28 cases of malaria.

2. It was found to bring down the temperature to normal in an average period of 29.9 hours, and to make the peripheral blood free from the asexual forms of malarial parasites by the third day.

3. The relapse rate was found to vary with the dosage of camoquin. A dosage of over 10 mg./Kg. was most effective in this respect.

4. A single effective dose of 0.6 Gm. is suggested for an average adult.

5. Three types of temperature charts were seen under the effect of a single dose of camoquin in malaria.

6. Camoquin, except for its relative expensiveness, should be preferred to paludrine, mepacrine and the other older anti-malarial drugs in the treatment of acute attacks of malaria.

ACKNOWLEDGMENT

My thanks are due to Parke Davis Company who were kind enough to supply me with camoquin in 1948 when it was not available in the market.

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ORIGINAL ARTICLE

RENAL TRIAD AND CORTICAL ISCHEMIA †

S. N. De *

The renal triad of oliguria and/or anuria, azotemia and tubular degeneration in the kidneys has long been known to the clinician and to the morbid histologist to be associated with diverse pathological conditions in man. As many as sixty causes, medical, surgical and obstetrical, have been listed and more are being added to the list. Some of these are associated with myolysis or hemolysis, *e. g.*, blackwater fever, mismatched transfusion, crush syndrome, burns, *etc.*, while in most instances no such liberation of myoglobin or hemoglobin occurs, *e. g.*, cholera, eclampsia, heat stroke and surgical shock. The blood pressure is often low especially at the beginning though it may be normal or even raised, *e.g.*, eclampsia.

The tubular damage has been ascribed by various authorities to three different causes :—(1) toxic substances—products of tissue injury especially uric acid and phosphoric acid[7], adenosine triphosphate[12], bacterial toxin, *e. g.*, in infected burns or injury and sulpha crystals[9]. (2) products of myo or hemolysis (pigment casts) deposited in the lower parts of the nephron[2] and (3) renal anoxia[10,13,14,15].

The oliguria and/or anuria together with azotemia has received three explanations—(1) blockage of tubules by precipitated pigments and debris in the lower parts of the nephron—rise in intratubular pressure—prevention of formation of glomerular filtrate[1]. (2) damage of tubules—unselective reabsorption of glomerular filtrate[3,7] and (3) renal ischemia—glomeruli deprived of blood reduction of glomerular filtration ; (a) pre-renal deviation of blood because less blood reaches the kidneys as a result of shock and hypotension[4], (b) cortico-medullary diversion of the renal blood which finds its way into the medulla leaving the cortex pale and ischemic[10,14,15].

Three names have been suggested for this type of renal pathology—

(i) Acute tubular necrosis : London School—Professor Dible.[6]
(ii) Lower nephron nephrosis—American Army School—Colonel Lucke[8].
(iii) Renal anoxia—Liverpool School—Professor Maegraith[11].

Working with my curator Sengupta[5], I have studied several kidneys in gross, by ordinary stains and by Pickworth's stain for blood vessels. Cases of burns, eclampsia, cholera, copper sulphate poisoning and others have been included in this study. The patients never survived for more than seventy-two hours after the attack. We have found that: (1) the tubules are not always necrotic,—cloudy swelling and fatty change may be the only signs of damage especially in earlier cases. Therefore we think that acute tubular necrosis is not a happy term. (2) The degeneration or necrosis is distributed, not in terms of first or second convoluted tubules or of the ascending or descending limb. The damage may involve both of each. Further, no pigment cast has been seen in the lower nephron. Therefore, the term lower nephron nephrosis does not appear suitable for these renal changes. (3) There is pallor of the renal cortex and congestion of the medulla in gross, which suggests active diversion of blood from cortex to medulla instead of simple pre-renal deviation of blood, in which case both the cortex and the medulla should have been pale. (4) In the Pickworth stained material for the demonstration of blood containing vessels, there is clear histological evidence of the occurrence of shunting or diversion of blood from the cortex to the medulla in these human kidneys. So far, such clear histological demonstration of cortico-medullary diversion had been possible only in animal kidneys[15]. (5) The site of parenchymatous damage corresponds to the site of ischemia,—the engorged medulla for the most part escapes any damage. (6) There is a fair degree of correlation between the degree of degeneration of tubules and the duration and intensity of ischemia of the cortex.

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† Paper read at the Conference of the Associations of Pathologists of India, held at Hyderabad, in November 1951.

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For these reasons, I would favour Professor Maegraith's conception of renal anoxia as the basic factor in this type of renal pathology, although I would like to be more precise and call it cortical ischemia. It explains the renal damage, its distribution and also the oliguria and azotemia at the same time.

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CASE REPORT

CHYLURIA

A REPORT OF TWO CASES TREATED WITH SODIUM PENTAVALENT ANTIMONY GLUCONATE

J. C. Patel *

From recent work, two drugs stand out as most effective in the treatment of filariasis. They are the pentavalent antimony compounds and an organic drug—diethylcarbamazine which is available to us in the form of hetrazan (Lederle) or banocide (Burroughs Wellcome). Antimony, when given in an adequate concentration for an adequate length of time, produces a lethal effect on the adult filarial worm, with the result that microfilaria in the peripheral blood persist for some time even after the adult worm has been killed. Diethylcarbamazine, on the other hand, acts on the microfilaria and has mild action on the adult worm. In the majority of the cases treated with diethylcarbamazine, microfilaria disappear rapidly from the peripheral blood but in a small percentage of people they might persist for a long period.

Among the pentavalent antimony compounds, neostibosan was considered most effective by Culbertson and his colleagues[1] in America, and Hawkings and his colleagues[3] in England. Culbertson[1] considered sodium pentavalent antimony gluconate (solustibosan) as the least toxic drug. Hawkings[3], in his experimental work, also agreed with him, but the effect on the microfilaria was not as good as with neostibosan. Goodwin and Page[2] have sometime ago studied the excretion of various antimony compounds and found that solustibosan was excreted rapidly, 90 per cent of the drug being excreted within 24 hours. In order to produce an adequate concentration of solustibosan in the blood for its effect on the adult filaria, the total dose of the drug would be required in increased quantities and it would, therefore, have to be given at frequent intervals. This aspect of sodium pentavalent antimony gluconate was not taken into consideration by Culbertson[1] in the treatment of five patients with solustibosan where he used 15 Gm. of the drug in 11-13 days.

Below are the case reports of patients suffering from chyluria treated with sodium pentavalent antimony gluconate in higher dosages for a prolonged period.

CASE REPORTS

Case 1. Mrs. D., aged 22 years, was seen for milky coloured urine of six months' duration. She was referred by an obstetrician as she was four months pregnant. There was no history of any other manifestation of filarial infection. On physical examination, nothing abnormal was detected. Her blood pressure was normal. Urine examination showed that it was mixed with chyle containing microfilaria. She was treated with sodium pentavalent antimony gluconate. The dose was 15 cc. (each cc. contained 20 mg. of antimony) twice a day for period of 21 days. With this treatment, she had a miscarriage which was attended to and from which she recovered without any complication. The chyluria persisted for about 16 days after completion of treatment, after which it stopped. She was followed up for a period of 12 months without any recurrence.

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* From, King Edward Memorial Hospital, Bombay 12.

Comment :—It is considered that sodium pentavalent antimony gluconate was responsible for curing the chyluria in this patient as well as for causing the miscarriage. The patient conceived later on.

Case 2. A male aged 36 was admitted to the King Edward Memorial Hospital for chyluria of three months' duration. There were no other manifestations of filarial infection or other abnormal physical signs. The examination of urine confirmed the presence of chyle. There were microfilaria in the centrifuged deposit of the urine. He was treated with sodium pentavalent antimony gluconate. The dose given to him was 20 cc. twice a day, intramuscularly, for a period of 14 days. On the tenth day, his urine cleared and remained free from chyle for a follow-up period of six months.

Comment :—The cure of chyluria in this patient was definitely due to the treatment with pentavalent antimony.

DISCUSSION

Chyluria has been treated with antimony in the past by a number of workers (Sherwani[4]) but the dosage was small and this was before the comparative rate of excretion of various antimony compounds was known.

The work carried out by Culbertson[1] in the treatment of filariasis does not take into account the rapid excretion of the sodium pentavalent antimony gluconate and his result with the drugs are not as good as that with neostibosan.

Further work should be carried out with larger doses of sodium pentavalent antimony gluconate in the treatment of filariasis. The two cases cited above bear this out, where large doses of sodium pentavalent antimony gluconate produced optimum concentrations of the drug in the blood and successfully cured the condition.

SUMMARY

Two cases of chyluria successfully treated with sodium pentavalent antimony gluconate are reported.

ACKNOWLEDGMENT

We take this opportunity of thanking Glaxo Laboratories for the free supply of sodium pentavalent antimony gluconate (Stibatin), and the Dean, K. E. M. Hospital, Bombay 12, for facilities.

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A NOTE ON LEPROSY RESEARCH CARRIED OUT IN BOMBAY *

STUDY OF EARLY LESIONS

(*a*) *Histological* :—Light has been thrown on the essential features of the pathogenesis of leprosy, which have hitherto been obscure, by the work of Dr. Khanolkar.

The infecting organisms have been followed from the prelesion stage, or silent phase of the disease, *i. e.*, contacts without lesions but positive for bacilli in the skin, to the stage when lesions appear, and it has been shown that the bacilli enter through healthy or slightly altered skin and find their way anywhere under the epidermis through the intercommunicating superficial lymphatic network. Later, the bacilli are attracted towards the degenerating and regenerating nerve fibres in the cutaneous plexuses, a process which occurs normally, and spread, in or along the nerve fibres. Hence the conclusion is reached that all leprosy is neural in its inception. In early neural lesions, the bacilli are seen in the remnants of nerve fibres and in the cellular exudate invading and investing the nerves, whereas, in the early or prelepromatous lesions, the bacilli are found only in the nerves and often in the finest nerve twigs, and, inspite of the presence of a large number of bacilli in the nerves, only a very slight cellular response either in the endoneurium or in the perineural tissue can be found. From here the bacilli burst out and disseminate into the dermal tissue to form lepromatous lesions.

In sulphone treated lepromatous cases negative to ordinary methods of examination, acid-fast bacilli and granules could be found in the nerve fibres.

Further study of the affected skin and nerves is being undertaken.

(*b*) *Clinical and Immunological* :—Further evidence that all leprosy is neural in its inception has been shown by the positivity of the positive bacillary contacts of leprosy cases to the lepromin test and the development of lesions from some of these contacts. The lesions that have developed so far have been observed to be of the neural type. Lepromatous lesions have not yet been seen to arise either from the positive or the negative contacts. During the current year, 131 contacts without lesions were tested with lepromin, and 47 gave a positive reaction. Of the 47, twenty-five were adults and 22 were children. In all these 47 lepromin positive contacts, 3 to 10 acid-fast bacilli were detected in smears made from the skin. Of the 84 lepromin negative contacts, 78 were negative for bacilli and 6 were positive for bacilli in the skin. These 6 were children.

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* Paper submitted to the Leprosy Advisory Committee of the Indian Council of Medical Research at Hyderabad in 1951, and read by Dr. N. Figueredo of the Acworth Leprosy Home, Matunga, Bombay.

LEPROMIN TEST

There is reason to believe that the reaction of healthy or apparently healthy persons to the Mitsuda, Fernandes and Dharmendra lepromin are dissimilar. Rotberg found that over 80 per cent of non-contacts gave a positive reaction to Mitsuda's lepromin, whereas only 28.7 per cent were positive to Fernandes' lepromin. In Bombay we have found that only 35 per cent (47 out of 131 examined clinically and bacteriologically) of contacts gave a positive reaction to refined lepromin (*vide* Appendix I), whereas over 80 per cent of persons living in an endemic area were found positive to Mitsuda's lepromin by the Calcutta workers.

It has been the practice in the A. L. Home for over 8 years to use a standard lepromin. The method of preparation of this lepromin is given in Appendix I. No originality is claimed for this method which is based on the work of others and our own experience. The use of this lepromin is recommended in studies on contacts if results are to be evaluated and compared at different centres.

SPREAD OF LEPROSY

With a view to obtaining data on the spread of leprosy from neural cases, clinical and bacteriological examination of members of households where only neural cases exist, and where no lepromatous case can be found in the neighbourhood, are being conducted in Bombay. Particular note is taken of new cases arising in such households during fixed periods of observation.

Preliminary work done has shown that 22.61 per cent (26 out of 115 examined clinically and bacteriologically) of contacts of lepromin positive neural cases who are in advanced stage of the disease, as compared to 28.28 per cent (28 out of 99 examined clinically and bacteriologically) of contacts of lepromatous patients have developed leprosy. Extended study is being conducted and all members of each household of neural cases are being examined periodically for further data on this subject, and the results compared with a similar study of households of lepromatous patients.

THERAPEUTICS

The following tables give the results of treatment with promin, sulphetrone, diasone and D. D. S.

Thiosemicarbazone :—Trials with this drug were commenced 6 months ago. As we feel that periods under 1 year are inadequate for the assessment of therapeutic results, details of this trial are not given.

TABLE 1.—*Results of Treatment.*

Treatment.	Type.	No. of cases treated.	Clinical improvement.*		Bacteriological improvement.@	
			1—2 years.	2—4 years.	1—2 years.	2—4 years.
Promin— 2 Gm. every day in neural and 5 Gm. daily in lepromatous cases.	Neural	37	18 out of 27	9 out of 10	2 rendered negative out of 3 positive.	5 rendered negative out of 8 positive.
	Leproma.	57	13 out of 32	20 out of 25	3 marked reduction. 1 negative.	10 marked reduction. 2 negative.
Sulphetrone— 2 Gm. 3 times a week by injection.	Neural	269	66 out of 252	16 out of 17	25 rendered negative out of 81 positive.	8 rendered negative out of 9 positive.
	Leproma.	149	48 out of 131	14 out of 18	16 marked reduction. 8 negative.	3 marked reduction. 3 negative.
Diasone— 1. Gm. 3 times a week by *injection.*	Neural	135	56 out of 131	3 out of 4	30 rendered negative out of 69 positive.	2 rendered negative out of 3 positive.
	Leproma.	117	52 out of 106	6 out of 11	16 marked reduction. 4 negative.	2 marked reduction. 2 negative.

* Clinical improvement in:

(*a*) Neural : Subsidence of thickened macules, erythema, subsidence of thickened and tender nerves.

(b) Lepromatous : Subsidence of infiltrations macules and nodules, healing of ulcers and eye complications.

@ Bacteriological improvement :

Marked reduction=From 5 bacilli in the whole smear to 1 in every field.

Negative=No bacilli detected in the whole smear from skin, ear-lobe and nose.

TABLE 2.—*Results with Diamino-Diphenyl-Sulphone*

Diamino-Diphenyl-Sulphone (Siegfried) tablets of 50 mg. each.

Dose : 1st week 25 mg.
2nd week 50 mg.
3rd week 75 mg.
4th week
and onwards 100 mg.
} a day for 6 days of the week.

No. of patients : 10

Type : L2N2. (Lepromatous infiltrations, nodules, thickening of ears. Anesthesia of hands and feet).

Period of treatment : 7 patients treated for 17 months.
2 patients treated for 10 months.
1 patient treated for 4 months.

Improvement in :—

Clinical condition: All the 9 patients treated from 10 to 17 months show a marked subsidence of nodules and infiltrations and healing of ulcers. Sensory changes not affected.

Bacteriological status : 4 out of 9 patients treated for 10—17 months show a considerable reduction in the number of bacilli (from 5 to 10 bacilli in every field now).

Blood : One patient who received 4 months' treatment only and whose red bloo cell count was 3.3 million developed severe anemia. He abandoned treatment. The remaining 9 patients did not show any appreciable change in the blood counts and hemoglobin content.

Reaction : 5 patients suffered from mild attacks of reaction.
1 patient suffered from acute orchitis and dermatitis.

CONTROL OF LEPROSY

Recent developments in the treatment of leprosy with D. D. S., oral and injectable, make possible mass treatment of patients with sulphones. Hence it is practicable to put into practice the suggestion of Dr. Pandit to treat all infectious cases with a view to reducing infectivity. In Bombay, a start has been made in this direction. Almost all our patients, including neural cases, are under treatment with sulphones, the majority on D. D. S. ; 1,650 patients are now receiving sulphone treatment.

BACTERIOLOGICAL EXAMINATION

Work in Bombay shows that the slit and scrape method is inferior in results, in neural cases and in contacts, to the skin biopsy method of examination (Method I, Appendix II). Experimental work for the easy demonstration of a large number of bacilli in neural cases and in contacts are being carried out. That the present methods for the detection of bacilli are inadequate can be seen from the work of Dr. Khanolkar who was able to demonstrate in sections fairly large numbers of bacilli in the nerves of sulphone-treated lepromatous cases, who by ordinary methods of examination were negative for bacilli. The improved methods, 3 in number, for the detection of bacilli, tried so far, are detailed in Appendix I. For a comparison of the results by the 3 methods, a piece of skin lesion larger than usual, was taken from neural cases and divided approximately into 3 equal parts on a slide. Examination of each case by the 3 methods showed that larger number of bacilli were seen in the smear by method II than by method I, and a still larger number by method III.

APPENDIX I

Preparation of Refined Lepromin.

Nodules are cut from lepromatous patients and autoclaved at 25 lb. pressure for 1 hour. The nodules are next finely minced in an ordinary domestic meat mincer.

The minced mass is placed in a glass mortar and ground in chloroform containing 2.2 per cent acetone, with a glass pestle. Small quantities of the minced tissue are taken up for grinding at a time. As the grinding proceeds the supernatant chloroform is pipetted off from time to time and collected in a glass flask and more chloroform added with further grinding.

4 oz. of the chloroform-acetone mixture will extract almost all the bacilli from 1 oz. of the minced tissue. The chloroform collected in the glass flask is poured into a porcelain dish and evaporated over a water bath. The residue, after evaporation, consists of a gelatinous mass spread out over the base of the dish. A smear from this substance should not show any tissue.

Sulphuric ether (30 cc. for 1 oz. of minced nodules) is added to the gelatinous material and stirred with a glass rod. This ether is poured into centrifuge tubes ad centrifugalised at 3,000 r.p.m. for 15 minutes. The supernatant ether is decanted into other centrifuge tubes and the tubes containing the deposit are placed in a desiccator. The decanted ether is subjected to centrifugalisation at 3,000 r.p.m. for 15 minutes. The supernatant ether is discarded and the tubes with the deposit are placed in a desiccator. The deposits in the various tubes are allowed to remain in the desiccator for 4 to 5 days. At the end of this period the deposits which are now dry and hard to some extent are separated from the bottom, by tapping the tubes lightly, and collected in a small glass mortar and ground with a glass pestle for about 5 minutes. This powder is stored in sealed ampoules.

For the preparation of the lepromin suspension, 10 mg. of the powder are ground in 100 cc. of normal saline in a glass mortar with a glass pestle using small quantities of the saline at a time. During the process of grinding a few drops of N/10 NaOH are added. A total of 15 to 20 drops are used for 100 cc. of the suspension. Carbolic acid 0.5 cc. is next added and the suspension is kept in ampoules and sterilised in an autoclave at 10 lb. pressure for half an hour.

Neither the dry powder nor the suspension is stored for a period longer than 6 months as in our experience it deteriorates after this period.

Dose:—0.1 cc. is injected intradermally in the skin of the forearm.

Reading of Results :—Experience shows that an early reaction of 5 mm. diameter gives a late reaction (nodule) of 3 mm. diameter. This is the minimum positive reaction. The maximum positive reaction observed (in tuberculoid cases) have been early reactions of 30 mm. diameter with a late reaction (nodule) of 8 mm. diameter. In such strong reactions, caseation and scab formation have been seen. It has also been found that the early reaction consists of an area of erythema, with edema more in the centre than at the periphery. The peripheral erythema and edema disappear after 48 to 72 hours but the central edema persists and gradually forms a nodule,—the late reaction—after a lapse of 3 weeks.

APPENDIX II

Methods for the Detection of Bacilli.

Taking of Biopsy :—The skin after being wiped with 5 per cent carbolic lotion is pinched between the blades of a forceps and an incision is made with a sharp scalpel deep into the corium. Another incision about 3 mm. apart is made at an angle of 25° to the first so as to meet the base of the incision in the corium and the wedge-shaped piece of skin removed.

Extraction of Bacilli—Method I :—The piece of skin is placed on a slide and is immediately pressed flat with the blade of the scalpel and with a rotary motion a smear is made. The flattened tissue is then rejected. The smear is fixed by heating very gently over a bunsen burner. This is the routine method adopted in the A. L. Home.

Method II :—The same process as in method I is adopted except that 4 to 6 drops of chloroform containing 2.5 per cent acetone, are dropped on the tissue before subjecting it to pressure with the blade of the scalpel.

Method III :—The piece of skin is placed in a centrifuge tube containing 2 cc. of chloroform (with 2.5% acetone) and allowed to soak for 4 hours. With a glass rod the tissue is pressed against the side of the tube with a slight rotary motion, under the surface of the chloroform till the piece of skin is flattened out. The tissue is then rejected. The tube containing the chloroform is evaporated over a water bath till only a few drops remain. When cool, about 5 cc. of sulphuric ether are added and centrifugalised at 3,000 r.p.m. for 5 minutes. The ether is next decanted leaving a few drops at the bottom of the tube. These drops are stirred with a platinum wire and poured drop by drop from the tube on a slide and a smear is made. A few drops of ether are added to the tube, to wash out the residue, and these drops are added drop by drop to the smear. The residue in the tube is washed out a second time with a few drops of ether. The smear dries quickly and is fixed by warming over the flame of a spirit lamp.

This smear consists of bacilli and fatty substance with a very small amount of tissue.

Staining :—Ziehl-Neelsen's method is adopted for method I.

For methods II and III, the carbol fuchsin is allowed to flood the smear for 25 to 30 minutes without heating at any time.

The decolourising is done with 10 per cent hydrochloric acid in distilled water without alcohol or rectified spirit.

Counterstain used is a dilute solution (2 drops in 5 cc. distilled water) of methylene blue, 1 percent in distilled water.

CURRENT MEDICAL LITERATURE

MEDICINE

TREATMENT OF MENINGITIS BY INTRACISTERNAL INJECTION OF CHLORAMPHENICOL. Trinidade, O., and Nastari, F. : J.A.M.A., 147 : 1757-1759, 1952. 1 reference.

The authors present a case report of a patient suffering from a severe *Shigella paradysenteriae* meningitis following spinal anesthesia where they administered chloramphenicol (chloromycetin) intracisternally and obtained successful results. The suspension used was 0.25 Gm. of chloramphenicol in 20 cc. of isotonic sodium chloride solution and 5 cc. of this was administered intracisternally. The chloramphenicol content of this dose was 62.5 mg. or approximately 1 mg. per Kg. of body weight. Within 24 hours of administration of this dose, the clinical picture was completely changed, the patient being almost cured. The case reported here suggests a new route of administration of chloramphenicol to humans and the authors recommend the intracisternal route because the antibiotic can be easily sterilised by boiling and possesses low toxicity.

ERIC COELHO.

CLINICAL EXPERIENCE WITH THE ANTICOAGULANT, TROMEXAN, Bronstein, M. R., and Witkind, E. : Am. J. Med. Sc., 222 : 677-685, 1952, 1 table, 2 figs. and 15 references.

Tromexan (3, 3-carboxymethylene-bis- (4-hydroxy-coumarin) ethyl ester), originally synthesised by Rosicky, in 1944, was tried by the authors in 22 cases of myocardial infarcts, 17 cases of thrombophlebitis, 3 cases of frost-bite, 5 cases of cerebral thrombosis, 1 case of postoperative mesenteric thrombosis of pulmonary embolism and 1 of peripheral arterial embolism. The prothrombin time was determined in each patient before beginning the treatment and daily during the course of the treatment. The duration of the therapy ranged from 2 to 46 days ; the initial dose of tromexan in most cases ranged from 1,500 to 1,800 mg. and the therapeutic prothrombin time was attained within 24 hours ; the second dose, after 24 hours, ranged from 600 to 900 mg. and occasionally 1,200 mg. in resistant cases ; the daily maintenance dose, after the first 48 hours, was 300 to 900 mg. and in some instances as low as 150 mg. An attempt was made to maintain the prothrombin time between 28 and 45 seconds. A transitory cumulative effect noted in 15 cases, disappeared in 24 hours on omission of the drug for a day. In 9 cases treated with 30 to 75 mg. of water soluble Vit. K, the prothrombin time decreased by 13.3 seconds in 4 cases during the first 24 hours. The prothrombin time decreased by 14.5 seconds on an average in 18 cases where tromexan was omitted for 24 hours ; in 5 cases where Vit. K was administered after the omission of the drug, the prothrombin time decreased by 23.4 seconds. Thirty-one patients received 20,000 units of repository heparin in addition to tromexan ; no untoward effect or increase in prothrombin time was noticed in any of the patients when both the drugs were administered simultaneously. Among the toxic effects, microscopic hematuria was noticed in 4 cases, gastrointestinal bleeding, persisting for 24 hours in 1 case, ecchymosis at the site of the injections in 2 patients, nausea and vomiting were frequently observed in most of the cases. In the author's opinion tromexan appears to be safer, and in many respects, a more advantageous preparation than dicoumarol. It is absolutely necessary to carry out the prothrombin determination daily during the first week of the treatment.

N. J. KOTHARI.

PSYCHOLOGICAL RESPONSE TO CORTICOTROPHIN, CORTISONE AND RELATED STEROID SUBSTANCES, Rome, H. P., and Braceland, F. J. : J.A.M.A., 148 : 27-30, 1952. 22 references.

In this article the authors report psychological reactions appearing in 4 patients treated with cortisone and in 1 treated with corticotrophin. The patient, when treated with a total dose of 2.2 Gm., developed marked catatonic stupor, which progressed to unmanageable excitement ; the second patient, treated with 3.8 Gm. of cortisone, developed paranoid-schizophrenic symptoms ; the third patient developed the same type of reaction as the second patient ; he had delusions of death, of being crucified and becoming God. The fourth patient developed a reactive depression with 1,500 mg. of cortisone ; he was greatly worried about his disease, tearful and anxious. The fifth patient showed a hypomanic paranoidal reaction with 400 mg. of cortisone; there was marked insomnia, pressure of speech and thought, flight of ideas, vivid dreams, phantasies, suspiciousness and irritability. The psychological response to cortisone or corticotrophin may vary widely, from a mild change in behaviour to symptoms of insanity ; there is no consistent corelation between the metabolic changes produced by hormones and psychiatric syndromes. Patients with psoriasis, chronic ulcerative colitis, gout, various allergic disorders and Addison's disease, are susceptible to psychiatric disturbances and complications, feeling of a extreme well-being, or that of extreme wretchedness and delusions of persecution are some the symptoms noted in cases of Cushing's Syndrome. The administration of steroid hormones brings about hyperplasia of the adrenal cortex, which evokes stress, leading to physiological as well as psychological changes ; the consequences depend on the patient's adjustment to his internal as well as external environments and the wide range of variation in psychological response is equated with the quantitative response to stress.

N. J. KOTHARI.

SURGERY

ADVANCES IN ORTHOPEDICS, Platt, Sir H. : Practitioner, 167 : 412-417, 1951. 25 references.

From the vast field of recent contributions to orthopedic practice, the author has selected a few topics which he has considered especially deserving of commentary.

Reconstructive Surgery of Joints :—Striking innovations in the technique of arthrodesis have minimised the high proportion of failures encountered by the older methods. The two types of arthrodesis devised by Brittain—the original ischio-femoral arthrodesis and the V-type, combining graft and nail, have provided a safe and precise methods of rapid fixation. The essentials of pseudoarthrosis have had their usefulness established by the late G. R. Girdlestone and the special technique devised by Batchelor, constitutes a notable addition. In arthroplasty proper, though little favour has been found among English Surgeons, considerable success has been obtained in the United States. Greatly improved results have been obtained with the use of nylon sheeting over the lower end of the femur. The use of arcylic resin prostheses has been of value in the reconstruction of joints and the great majority have so far been carried out on the hip.

The Bone Bank :—Only in recent years has homogeneous bone, preserved under conditions of cold storage, been freely used in preference to autogenous bone. It has been advised that the stored bone should be used within a year of its deposit in the bank.

Internal Fixation of Fractures :—The Kuntscher intramedullary nail was enthusiastically adopted by Bohler, at first limited to the treatment of recent fractures, it was extended to cases of non-union and delayed union. Its limitations are now fully appreciated but, nevertheless, it remains the outstanding technical advance in the operative treatment of fractures. It can be safely used in pathological fractures due to Paget's disease or even due to secondary deposits. It is often a convenient method of controlling an ununited fracture in combination with a bone graft.

Mechanical Control of Bone Growth :—Controlled method of attack on the growing epiphysis was evolved by Blount and Clarke for temporary arrest of growth in length at the knee by the insertion of staples which penetrate the bone above and below the growth disc. After the removal of the staples the epiphysial growth is resumed at the normal rate.

The Cause of Congenital Deformities :—Interest has been awakened by the remarkable experimental observations of Duraiswami who has been able to produce in the chick embryo, by the injection of insulin in the yolk, a range of skeletal abnormalities depending on the date and intensity of the injection.

EUSTACE J. DE SOUZA.

ADVANCES IN ANESTHESIA, Gillies, J. : Practitioner 167 : 418-423, 1951.

The subject is discussed from the point of recent developments mainly in respect of their suitability for adoption by part-time anesthetists especially those who combine an anesthetic appointment with general practice.

Ether and chloroform have long been the standby, but despite their reputation, effective anesthesia to satisfy the needs of modern surgery is difficulty to obtain without the newer refinements in technique and modern specialised apparatus.

Tracheal intubation is a worthwhile accomplishment and almost a necessity in certain emergencies, especially where there is the danger of a copious reflux of fluid from the stomach during the induction of anesthesia. Gastric lavage before and tracheal intubation after induction are essential measures. The clear airway which the intratracheal tube provides makes for quiet and unobtrusive breathing. The absorbtion of carbon dioxide with a closed circuit machine and the additional safety and relative freedom from post-anesthetic morbidity are outstanding improvements in inhalation anesthesia.

Intravenous anesthesia has made a popular demand which is difficult to resist but a high degree of proficiency is essential and the limitations must be clearly realized.

Muscular relaxants have vastly changed the scope of anesthesia and though there are many reliable preparations the original d-tubocurarine chloride has not been excelled. Curarization must be limited so far as possible to the period during which relaxation is needed and no longer. Detoxification of tubarine can be accelerated if necessary by the intravenous injection of prostigmine and atropine.

Controlled hypotension is of considerable interest as a means of reducing bleeding during surgery but is only justifiable when competent management can be ensured.

EUSTACE J. DE SOUZA.

GASTROINTESTINAL ALLERGY SIMULATING REGIONAL ENTERITIS, Blumstein, G. I., and Johnson, J.: J.A.M.A., 147 : 1441-1443, 1951.

The relationship between the offending allergen and the onset of symptoms are usually recognised in attacks of gastrointestinal allergy and since the signs and symptoms seldom warrant surgical intervention the bowel is rarely visualised during such attacks. However, if such an abdomen is opened, the only change, if any, is one of mild edema of the bowel. The authors report such a case where a male, aged 26, was subject to bouts of abdominal distress and was operated upon during such an attack because of a presumptive diagnosis of recurrent acute appendicitis. The terminal ileum was involved by what appeared to be reasonably regional enteritis. After resection the histological picture was found to be typical of an allergic reaction. There was marked submucous and subserous edema and massive eosinophilic infiltration. He made an uneventful recovery but subsequently had three similar episodes of abdominal pain after the ingestion of seafood. On refraining from this type of food he has remained free from symptoms. The clinical diagnosis in such cases is usually easy but is not considered valid unless there is a cause and effect relationship between the offending allergen and gastrointestinal symptoms. Peripheral eosinophilia, or the roentgen demonstration of gastric retention, abnormal intestinal mobility with segmentation of the small bowel and decreased lumenal caliber should arouse suspicion of allergic involvement of the gastrointestinal tract. That the ileum is able to act as a 'shock organ' has been amply demonstrated by Gray, Harten and Walzer.

EUSTACE J. DE SOUZA.

A NEW TUBE FOR USE IN TREATMENT OF INTESTINAL OBSTRUCTION, Devine, J. W., Jr. : J.A.M.A., 148 : 115-116, 1952.

The author briefly reviews the various tubes that have been used in the problems of decompression of the intestine in the presence of obstruction. The main difficulty has been the impossibility of maintaining a constant drainage, as the suction creates a negative pressure sufficient to cause the intestine to collapse around the tube. Thus one loop may be evacuated but as soon as this is accomplished the mucosa is sucked against all the available holes. To overcome this, the author has developed a tube-within-a-tube which prevents the vacuum mucosa obstruction phenomenon by the application of the principle of the air vent. This is clearly seen in the author's diagram. A clear plastic tube is used with approximately 100 small holes extending over a distance of 25 cm. to within 1.5 cm. of the closed distal end. Into the outer tube a small diameter polyethylene tube is inserted for the entire length. A T-shaped glass connector is inserted into the upper end and the straight end is closed off with a rubber diaphragm through which a hypodermic needle is inserted to make a tight junction with the polyethylene tube. Suction is applied to the other branch of the T-tube and the polyethylene tube provides the air vent through which the atmospheric air is sucked into the intestine preventing the mucosa from collapsing over the holes in the outer tube. Occasionally it is desirable to apply the suction to the inner tube, thus using the principle of an intralumen sump suction which, however, drains at a slower rate. The author has found the most efficient tube to be one that has the inner tube one third the diameter of the outer, and the hole in the outer should be of the same size as the lumen of the inner tube. A continuous motor suction of course must be used as the water bottle drainage type of suction would not be feasible. The author describes the various applications that this type of tube have, with or without modifications for individual requirements.

EUSTACE J. DE SOUZA.

PEDIATRICS

MALNUTRITION AND ANAEMIA IN YOUNG CHILDREN : CLINICAL STUDY OF FIFTY CASES, Price, J. P., Hart, W. M. : J.A.M.A., 148 : 5-10, 1952. 3 tables.

Though the American children are getting the best care, this study brings to light that during the latter part of the first year and during the second and third years of life, inadequate care is the immediate cause of malnutrition and anemia, which is primarily due to faulty foods containing insufficient iron and vitamins. A clinical study of malnutrition and anemia in 50 children is presented.

Milk is undoubtedly the best single food but by itself it is not a complete food and it was found that failure to wean a baby from breast or bottle during the last month of the first year was a frequent cause of malnutrition and anemia. The majority of the children seen with malnutrition and anemia were getting 4 bottles of 8 oz. daily. The baby satisfies himself with milk, refuses other foods, and goes on his anemic way, Failure to continue the administration of supplementary vitamins after the first few months and in the second year of life was also observed, as also poor understanding on the part of the parents as to what constitutes a satisfactory diet.

The treatment prescribed is dietetic, getting the child on a well-balanced diet and encouraging him to feed himself as much as possible, and milk should be given at the end of the feed, and feeding in between meals is discouraged. An iron vitamin mixture containing 4,500 I. U. of vitamin A, 40 mg. of thiamine hydrochloride, 1.8 mg riboflavin, 90 mg. ascorbic acid, 1,500 I. U. vitamin D and 150 mg. of ferrous sulphate daily, gave very good results. According to the authors, the amount of thiamine hydrochloride appears to be grossly excessive but clinical experience has proved to them its value in stimulating appetite. They are convinced, from several cases of beriberi seen, that thiamine deficiency is not uncommon. It is to be noted that the amount of vitamin A, riboflavin and ascorbic acid and vitamin D is three times the daily requirement recommended.

The problem of malnutrition and anemia in children is not merely of diagnosis and treatment but primarily one of prevention.

L. BANERJI.

THE DIRECT SURGICAL ATTACK ON PULMONARY STENOSIS, Downing, D. F., Fischer, C. C., Bailey, C. P., Glover, R. P., and O'Neill, T. J. E. : Journ. of Ped. 39 : 645-649, 1951. 7 references.

The authors present the results of pulmonary valvulotomy in a series of 30 consecutive cases of the tetralogy of Fallot, cases in whom the age ranged from 3 months to 36 years. Diagnosis of tetralogy was confirmed in 22 cases by angiocardiography; but this procedure was unsuccessful in 4 cases and not attempted in the remaining 4 because of the precarious state of the patients. The stenosis was valvular in 15 cases infundibular in 12, and confined to a segment of the pulmonary artery in 3. There were 7 deaths in the series (over-all mortality 23.3%), 5 of these occurred in the operating room and the remaining two, 5 hours and 13 weeks post-operatively, respectively. Of these seven patients, two had associated malformations of the brain and other organs, and another had hydrocephalus which may have contributed to their demise. Cyanosis was relieved simultaneously with the removal of obstruction to the pulmonary flow in all who left the operating room alive except two patients. Post-operative complications included pleural effusion which required thoracentesis (3 cases), pericardial effusion (2 cases) and cardiac failure (8 cases). Too early ambulation probably brought on cardiac failure in 5 of the 8 cases. The systolic murmur remained the same in some cases, in others became harsher, and in one case diminished in intensity ; temporary diastolic murmurs developed in 6 cases, five of whom developed temporary heart failure. Electrocardiographic tracings showed no constant changes.

The authors classify the results in 23 patients who survived as follows : 12 cases, (6 valvular stenosis, 3 infundibular and 3 localised constriction of pulmonary artery) excellent response : 7 cases, very good condition with increased exercise tolerance ; in the remaining 4 cases, the observation period has been too short. The authors recommend pulmonary valvulotomy in the treatment of pulmonary stenosis in the tetralogy of Fallot as this constitutes a direct approach to the removal of the obstruction in contrast to the shunt operations in which an artificial ductus is created thereby throwing an extra burden on the heart. They give a short resume of the surgical approach.

F. A. NAZARETH.

OPHTHALMOLOGY

STREPTOMYCIN IN OPHTHALMOLOGY, Sorsby, A., Ungar, J., and Bailey, N. L. : B.M.J. 1 : 119-123, 1952. 2 tables.

Tuberculous lesions of the eye and infections by gram-negative bacilli are the two groups for which streptomycin therapy is indicated. Infections by gram-negative bacilli are infrequent and they are caused by *P. pyocyanea* and *P. vulgaris* causing infection of the cornea. The ulcers are characteristic and they are not influenced by penicillin or the sulphonamides.

Tuberculosis of the conjunctiva, cornea, iris and retinal veins is secondary to a general infection, and in these cases local therapy is of some value but alone will not be satisfactory.

Experimental work on rabbits confirms that streptomycin 0.5 Gm. in 1 cc. of water is well tolerated on subconjunctival injection—even better than 1,000,000 units of penicillin, and such doses injected subconjunctivally produce much higher intraocular levels than intramuscular injections. When adrenaline 1 : 1000 is added, the intraocular levels are still higher and persist upto 16 hours.

A destructive *P. pyocyanea* infection of the cornea in the experimental anima was controlled by one subconjunctival injection of 0.5 Gm. of streptomycin in 1 cc. of adrenaline 1 : 1000.

For clinical purposes, streptomycin 0.5 Gm., should be dissolved in 10 minims (0.6 cc.) of water to which 5 minims (0.3 cc.) of adrenaline 1: 1000 is freshly added.

Gram-negative lesions of the cornea are highly destructive, so early treatment is essential and the characteristic clinical appearance facilitates early diagnosis. In acute conjunctivitis due to gram-negative bacilli, streptomycin locally is also invaluable.

Systemic streptomycin therapy has proved helpful in tuberculous keratitis but has given poor results in tuberculous iridocyclitis and in periphlebitis. In phlyctenular ophthalmia it tends to cut short severe attacks and reduces the frequency and severity of relapses.

L. BANERJI.

PROPHYLAXIS OF OPHTHALMIA NEONATORUM, Editorial : J.A.M.A., **148 : 122-123**, 1952.

Silver nitrate prophylaxis causes chemical conjunctivitis, and the stock solution used may become dangerously strong, causing organic damage to the cornea. Occasional mistakes, such as the use of a 10 per cent solution, have been made, and the infant blinded. Penicillin prophylaxis is equally efficacious and has none of the above objections. Against penicillin solution, the arguements used are that the ointments or solutions should be kept on ice and they deteriorate in time and, unless properly preserved and renewed, they become inactive and there is the possibility of sensitization to penicillin.

It is agreed that the parenteral injection of the mother before birth and of the baby after birth, or the topical application of the ointment effectively prevents ophthalmia neonatorum and eliminates chemical conjunctivitis.

There is the danger of an improperly preserved or old penicillin ointment becoming ineffective. The danger of sensitization by one application is so slight that it may be dismissed.

Those who are for silver nitrate prophylaxis argue that while 1 per cent silver nitrate causes chemical conjunctivitis in a high percentage of cases, such conjunctivitis is trivial and there is no record that properly prepared Crede prophylaxis causes harm to the infant's eye. Modern wax ampoules completely obviate the danger of evaporation and use of a wrong solution.

The reports and experience of various obstetric clinics clearly indicate that penicillin prophylaxis under proper control is superior to the established silver nitrate procedure ; nevertheless, no radical change in the existing laws or regulations regarding the silver nitrate prophylaxis should be recommended at this stage.

L. BANERJI.

As a general practitioner, my experience of psychiatry is wide rather than deep but not wide enough to reveal the psychosomatic implications of this patient's plea : "Oh Doctor, could you give me something not quite so strong for my constipation? I can't stand this perjury."—The Lancet, London. (Quoted from American Practitioner and Digest of Treatment, 2 : 700, 1951).

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2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

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ORIGINAL ARTICLE

ACUTE GENERALISED MILIARY TUBERCULOSIS IN ADULTS

K. S. Mathur and P. N. Wahi *

Acute generalised miliary tuberculosis, first described by Bayle[5] and Laennec[13] in 1810, is a condition of systemic generalisation affecting many organs of the body due to a sudden invasion of the blood stream from an established focus. Chapman and Whorton[7] laid down the criteria for the autopsy diagnosis of acute generalised miliary tuberculosis as follows : that the tubercles be acute, provoking little or no fibrous tissue reaction; that the disease sufficiently generalised to involve the liver, spleen and at least one additional tissue such as the lung, bone marrow or kidney; and that the tubercles be miliary in size. By and large, the same criteria have been adopted for the purposes of this paper.

The wide range of systemic generalisation of tuberculosis, which depends on the extent of dissemination and the size of the dose, has been excluded from consideration. When the number of organisms is large and the patient particularly susceptible, the spectacular condition '*sepsis tuberculose accutissima*' is said to occur. This condition is an extremely acute and generalised process resulting in death before miliary tubercles have had time to form. At autopsy small areas of necrosis, containing numerous tubercle bacilli with little or no cellular reaction, are found scattered throughout the body. The other extreme of systemic generalisation is the chronic disseminated form of tuberculosis. This represents a mitigated chronic type of generalised tuberculosis which has a definite tendency to heal by fibrosis and invariably tends to affect the lungs. In this condition, fibrous areas are scattered throughout the lungs, some of these still showing evidence of active infection. There is yet another form of the disease which is less common and less generally recognised, the general protracted multiform tuberculosis. In this condition, the dissemination is similar but occurs at varying times and in varying amounts. While all the organs of the body may be involved, the lesions instead of being uniform in size throughout, vary markedly in size, shape and character. The progress of the infection, also, is not acute.

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Acute generalised miliary tuberculosis is a rare condition. According to Fishberg[9], 5 per cent of patients with pulmonary tuberculosis die of acute miliary dissemination. Auerbach[3] reported 297 cases (17.9%) of this condition amongst 1,656 consecutive autopsies on tuberculous persons. Chapman and Whorton[7] reviewed autopsies on 4,066 patients. In 310 of these, tuberculosis of some sort was present. In this group there were 63 cases (20%) of acute generalised miliary tuberculosis.

The purpose of this paper is to study the clinical and pathological manifestations of this condition in Indians from a review of clinical and autopsy material of the last ten years at the Sarojini Naidu Hospital, Agra.

CLINICAL COURSE

The clinical course of acute generalised miliary tuberculosis is so variable that the diagnosis before death is often difficult, except in cases where a roentgenogram of the chest reveals the miliary spread.

The disease affects all ages, and even antenatal transmission of the disease has been suggested. After excluding cases in the first decade from consideration, the highest incidence was observed in the second decade, while cases in the third, fourth and fifth decade were equally divided. One patient was 53 years of age. The present series is not large enough to draw any conclusions, but the figures are in general agreement with those of Hartwich[10], Auerbach[3], and Chapman and Whorton[7], who also found that the disease was more frequent in the younger age group.

Both sexes are affected. In this series, 66.6 per cent were males and 33.4 per cent females. The preponderance of acute miliary tuberculosis in males was first observed by Litten[14], as early as 1875, and confirmed subsequently by Fishberg[9] and other workers[3],[7]. In Hartwich's series, the sex incidence was equal, with a slight preponderance of females (51%).

Fever was the commonest symptom (83%) and was accompanied with rigors in two cases. Cough was usually the second important symptom. This was often accompanied by expectoration. Cough and hemoptysis (25%) were the usual symptoms of associated pulmonary tuberculosis, although, cough alone was encountered in uncomplicated cases of acute miliary tuberculosis as well. Only in one case did the patient get bouts of dyspnea and cough for about a month before her death. Pain in the abdomen was the commonest (46%) abdominal symptom. Loss of appetite was frequently (38%) complained of. Irregularity of bowel movement was a symptom in only 33 per cent of cases. One half of whom had constipation and the other half loose motions or diarrhea. General weakness was the only presenting symptom in one case, although it was a complaint in 16 per cent of patients. Headache, drowsiness and vague pains in the calf muscles and legs were recorded in one case each. All cases diagnosed as tuberculous meningitis have been excluded from the present analysis. The most interesting clinical picture was presented by a Mohammedan male, aged 40 years, who was treated for pleurisy 3 months previously in jail On the day of discharge from jail after an apparent recovery, he became unconscious. He was delirious and the pupils were dilated, reacting sluggishly to light. He was suspected to be a victim of datura poisoning. He developed spastic paralysis of the right arm and hand while in the hospital. He was labelled as a case of encephalitis lethargica. The diagnosis of acute miliary tuberculosis of the lungs, spleen, liver, and meninges, was made at autopsy.

The physical findings were as variable as the symptoms and no signs could be said to be typical of this condition.

The course of the temperature was remittent in some, intermittent in others, and more generally, irregular. Hegler[11] described true hectic fever of the so called " picket fence " type in some of his cases, but found the irregular remittent type as the most frequent. We agree with Cornet[8] that there is no definite pattern of the temperature. Irregularity is its most characteristic feature. All patients without exception had tachycardia, the pulse rate usually varying between 100 and 120 per minute. Only in one case did the pulse rate remain about 150 per minute throughout his stay in the hospital. The respiratory rate was usually increased but there was no significant observation and no correlation between the extent of lung involvement and the rate of respiration.

The abnormal physical signs in the lungs were a more constant feature and were recorded in 83 per cent of cases. There was no fixed pattern of auscultatory findings. A few scattered rales or rhonchi, clinically inconclusive of any definite lesion, were heard in cases which were not associated with chronic pulmonary tuberculosis with definite signs of cavitation or exudation or fibrosis. Fifty per cent of cases showed varying degrees of chronic pulmonary tuberculosis in combination with the miliary dissemination. This is in conformity with the report of 191 of 297 cases reviewed by Auerbach[3], but does not agree with the view expressed by many other authors who supported Weigert[16] in his conviction that the presence of chronic pulmonary tuberculosis excludes or certainly lessens the chances of the development of acute miliary tuberculosis.

The blood pressure was low in all cases except one. In the case of a Hindu male, aged 16 years, triple rhythm was heard just internal to the mitral area at the time of admission and premature beats were noted two days before death. One case presented all the symptoms and signs of congestive heart failure, dyspnea, edema, engorged neck veins, basal congestion and an enlarged, tender liver. He was found to have a tuberculoma of the right auricle in addition to miliary spread. It will be described in some detail later.

The spleen was palpable in 16 per cent of cases and tenderness was recorded only in one case. Chapman and Whorton[7] reported 12 per cent of cases in which the spleen was palpable, and this agrees with the observation made by Amberson[1], that the spleen is palpable in a minority of cases. These reports are in variance with the findings of Litten,[14] who found the spleen palpable in 70 per cent of his cases. Hegler[11] agrees with this report. The liver was palpable in 33 per cent of the cases, and was tender in 3 cases. Generalised rigidity and tenderness of the abdomen was noticed in one case.

Cervical nodes on both sides were enlarged in one case, and the submental nodes were palpable in one other case.

LABORATORY INVESTIGATIONS

The total leucocyte count varied between 6,500 and 15,000 per c.mm. The count was above 10,000 in 44 per cent of cases and the same percentage had a count below 8,000, while only 12 per cent of cases had a count between 8,000 and 10,000 per c.mm. The differential count showed an increase of neutrophils, ranging between 70 and 90 per cent, except in one case associated with pulmonary tuberculosis were the neutrophils were only 54 per cent. The combination of leucopenia and relative neutrophils has been described as diagnostic by Warthin[15], and Chapman and Whorton[7]. Emphasis has been laid on the excessive demand for neutrophils, rather than on a defective supply, in explaining the leucocytic reaction.

The urine showed the presence of albumin in 50 per cent and the presence of pus cells in 30 per cent of cases. Hyaline and granular casts were reported only in one case.

PATHOLOGICAL FINDINGS

The gross anatomy of the various organs was studied for identification of miliary tubercles. These were not difficult to recognize in the lungs, kidney, liver and spleen. They were confirmed on routine microscopic serial sections.

Sometimes, their presence was recorded only under the microscope on account of their small size. This was particularly true of myocardial, adrenal and thyroid tubercles.

The lungs were affected by the acute miliary spread in 85 per cent of cases. These included two cases in which the gross appearance only suggested some congestion and it was not until histological sections were examined that the miliary tubercular lesions were seen. The most infrequent association of chronic pulmonary tuberculosis with the miliary spread has already been discussed. The weights of the lungs were increased even in uncomplicated cases of acute miliary tuberculosis. The maximum weight of the right lung was 487 Gm. (normal 450 Gm.) and that of the left lung 540 Gm. (normal 350 Gm.). The lungs retained their normal shape and reddish brown colour. On their surface were scattered small white nodules of the size of pinheads and some bigger in size upto 3 mm. Microscopically, scattered in the lung tissue were numerous tubercles with central caseation and surrounded by cellular infiltration of plasma cells, epitheloid cells and lymphocytes and the presence of characteristic giant cells. The neighbouring alveoli showed emphysema. The intervening lung tissue was fairly normal.

It is very rare for the heart to be involved although miliary tuberculosis of the pericardium is not so uncommon. Straw coloured pericardial fluid 90 cc. and 125 cc., were collected from two cases. There was one interesting case of a Hindu female, aged 45 years, who was diagnosed as congestive heart failure during life and whose autopsy was performed by one of us (P. N. W.). At autopsy, an irregular yellowish looking mass measuring 6.5 x 5.0 cm. was found inside the cavity of the right auricle occupying its anterosuperior wall as well as the interauricular septum. It was hard in consistency and the cut surface showed a granular caseating mass. The left auricle in the region of the aorta showed tubercles with caseation. A few whitish tubercles on the intimal surface of the aorta, close to the ostia of the coronary arteries, were seen. The portion of the growth in the right auricle, under the microscope, showed a typical tubercular granuloma with a typical central area of caseation surrounded by lymphocytic infiltration, typical foreign body giant cells and positive acid fast stain. The myocardium of the posterior wall of left auricle, pericardial surface of left ventricle, pericardial wedge between left auricle and left ventricle and the pericardial covering adjacent to the pulmonary valve and the right ventricle showed the tubercular granuloma. The cases of tuberculosis of the myocardium reported in literature include miliary, nodular and diffuse infiltrative forms. Horn and Saphir[12] reported 19 cases (0.24%) of tuberculosis of the myocardium in 7,683 autopsies of patients, who died of generalized tuberculosis. Auerbach and Guggenheim[2] found 29 such cases (0.28%) among 10,165 autopsies of tuberculous patients. Bose[6] had reported a case, in 1942, which he described as a tumour-like growth in the myocardium. The wall of the right auricle has been found to be the most common site of nodular tuberculosis by Anders[2].

Both the spleen and liver were involved in all cases. The weight of the spleen ranged between 93 Gm. and 186 Gm. (normal 120-150 Gm.)

and the liver weighed between 977 Gm. and 1,846 Gm. (normal 1,650). The heavy spleens and livers were not necessarily the same which were palpated clinically. The colour of the spleens was usually slate blue and the cut surface showed up dark red in colour. White miliary tubercles stood out prominently but in a few cases they were indistinguishable from the splenic corpuscles on gross examination. Malpighian bodies could always be made out separately. Under the microscope the trabeculae of the spleen were thickened and usually increased in number. In the pulp of the spleen were scattered many tubercles with central caseation, surrounded by cellular infiltration of lymphocytes, plasma cells and a few epitheloid cells and giant cells. Malpighian bodies did not show any involvement but they were usually few in number. There was usually congestion of the pulp sinusoids and infiltration with plasma cells, lymphocytes and epitheloid cells. The cut surface of the liver was usually congested and of a dark brown colour, with white pinhead sized nodules scattered all over. On microscopic examination, tubercles were seen in the substance of the liver. In the region of the tubercules, the liver cells were completely destroyed with central acidophilic necrotic masses, plasma cells, epitheloid cells and tubercular giant cells. Liver cells at the periphery of the tubercles showed fatty degeneration in a few cases.

The peritoneum was affected by the acute miliary tuberculosis in 71 per cent of cases, less than half of which presented amber coloured clear peritoneal fluid. Numerous white pinhead sized nodules were usually scattered all over the omentum. Tubercles were found on the peritoneal surface of the small and large intestines, mesentery, uterus, broad ligament and ovaries in different cases. In one case a Hindu male, aged 50 years, a large number of tubercles were found on the peritoneal coat of the appendix, and at one point the process could be seen extending into the muscular coat of the wall of the appendix.

The stomach and duodenum very rarely show evidence of acute miliary spread. During the present study, one example of each was met with in the same case of a Hindu male aged 30 years, who was labelled as a case of acute miliary tuberculosis with chronic bilateral fibrocaseous pulmonary tuberculosis. On gross examination, the walls of the stomach were normal. The rugae in the body of the stomach were prominent and there was a congestion of the mucous membrane near the pylorus, which was stenosed and showed thickening of its ring. Under the microscope, the mucosa showed diffuse tubercles, and at one place, the tubercle burst into the lumen producing an ulcer of the mucosa. The epithelial lining of the mucosa at the pyloric end was desquamated, destroyed, and showed lymphocytic infiltration. At some places the mucosa and submucosa were entirely destroyed by caseation and inflammatory cellular reaction. The duodenum had a normal arrangement of the longitudinal and circular muscle fibres. The columnar epithelium of the mucous coat was destroyed and showed diffuse lymphocytic infiltration. At places, there was a complete destruction by caseation surrounded by inflammatory cells. The Brunner's glands were seen in the submucosa, but were absent at some places due to caseation and lymphocytic infiltration.

Typical tubercular granulomata were found in the submucous tissue of the small intestine in 28 per cent of cases. The lower part of the ileum was usually affected. The cecum and ascending colon were involved in only one case each. Acute miliary tuberculosis of the appendix was recorded in two cases. In both cases, the serous layer covering the appendix and the mucous and submucous layers, showed caseating areas with a positive acid fast stain and lymphocytic infiltration and giant cells.

In generalized miliary dissemination one would expect to find miliary tubercles in the kidney as frequently as in the spleen and liver. But only 28 per cent of the present series presented typical tubercular granulomata. The urinary bladder had subperitoneal tubercles only in one case. Both suprarenals showed miliary tubercles, on the surface in one case, and deeper in the cortex, in another.

The commonest site for the acute miliary tubercles of the dura mater was on both sides of the longitudinal sinus. Small pinhead sized white nodules, raised above the surface, were observed in 42 per cent of cases. The surface of the dura mater was rough. In one case the dura mater covering the base of the brain showed marked congestion round the raised miliary tubercles. In the exudate of the subarachnoid meshwork and round the blood vessels, there were areas with definite tubercles which showed an acidophilic debris and a tendency to giant cell formation. The finding of a tuberculoma of the dura mater in one case is worth recording. It was a circular growth 1.5 x 0.25 cm., greyish white in colour and friable in consistency, producing a depression in the region of the post central gyrus in the lower part, 2 cm., above the lateral sinus. On histological examination, this was a tubercular granuloma with caseation, lymphocytic infiltration, and a tendency to giant cell formation. The patient had no nervous manifestations.

The enlargement of the nodes at one site or the other was invariably present. Hilar nodes were most frequently enlarged and often caseating. Mesenteric nodes were involved, next in frequency. The entire glandular structure was usually replaced by tubercular granulation tissue and, sometimes, the gland was studded with tubercles.

SUMMARY

The wide range of systemic generalization of tuberculosis have been analysed. Acute generalized miliary tuberculosis has been defined. The

clinical and autopsy material of the last ten years at the Sarojini Naidu Hospital, Agra, has been reviewed.

The age and sex distribution has been discussed. The frequency of symptoms and physical findings have been analysed. The diagnostic significance of relative neutrophilia has been described.

The gross anatomy and the microscopic findings in different organs affected by the acute miliary dissemination have been described and reference made to a few uncommon findings.

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ERRATA

In the article "Radiological Aspects of Bronchiectasis," by Madan Lal Aggarwal, (April 1952 Issue) the legend pertains to Fig. 7 and not to Fig. 8. The legend to Fig. 8 does not appear under it but is mentioned in the text.

ORIGINAL ARTICLE

CYTOLOGICAL DIAGNOSIS OF CERVICAL CANCER *

STUDY OF 300 CASES

P. N. Wahi † and R. L. Jain. †

In the present study two vaginal smears on an average have been studied in 300 patients. Among the 300 patients, 81 had malignancy of the uterus or cervix proved by histologic examination of tissue removed by biopsy or at operation. This included 73 squamous carcinoma of the cervix, 1 adeno-carcinoma of the uterus and 7 of the miscellaneous group. The cytology was in accordance with the histology in 76 cases. In 36 cases, cytology showed malignancy but the histology was not done and so it was not confirmed.

This group of 300 cases included 117 with positive or suggestive cytology, and 183 with negative cytology. (Table 1.)

Of the 117 cases with positive cytology or cytology suggestive of malignancy, the cytology was not confirmed by histology in 5 cases.

Of the 183 cases with negative cytology, the negative cytology was not confirmed by histology in 6 cases.

TABLE 1.—*Results on* 300 *Patients.*

Tests Performed	300
Cases with negative cytology	183
Cases with positive cytology	111
Cases with cytology suggestve of malignancy	6
Confirmed Cancers : positive cytology and positive pathology	76
Squamous cancer of cervix	71
Adenocarcinoma	1
Miscellaneous	4
Cytology not confirmed	36

False Positive.—Table 2, shows the details of 5 false positive cases. Case 1, on cytologic examination was labelled as an adenocarcinoma. Clinically the case was definitely malignant so much so that radium was applied to her without waiting for biopsy diagnosis, which later showed

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*Presented in the Seminar on "Exfoliative cytology in the diagnosis of Carcinoma", in the Annual Meeting of the Indian Association of Pathologists, at Hyderabad, on 23rd November, 1951.

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TABLE 2.—*False Positive Cytology. (Cases with Positive Cytology and Negative Pathology in* 300 *Patients*).

Clinical Diagnosis.	Smear Diagnosis.	Pathology.
1. Cancer Cervix ..	Adeno Carcinoma	Tuberculous Cervix.
2. Cancer Corpus ..	Cells Suggestive of Adeno Carcinoma	Endometrium-Cystic Hyperplasia.
3. Cancer Cervix ..	Epidermoid Carcinoma	No malignancy (Twice).
4. Cancer Cervix ..	Malignant cells present	No malignancy (Twice).
5. Early Cancer Cervix	Suspicious Malignant cells (Twice).	Chronic Cervicitis.

a tuberculous lesion. The case probably had both tuberculosis and coexistent carcinoma. In case 2, the cells were suggestive of adenocarcinoma of the endometrium but only cystic hyperplasia of the endometrium was detected. In case 3, cytology showed epidermoid carcinoma while biopsy done twice revealed no malignancy. In case 4, the cells were suggestive of malignancy while biopsy done twice did not show malignancy ; instead, there was marked epidermidization of the cervical glands. In the fifth case there were only suspicious malignant cells and no definite opinion was possible on smears taken twice. Biopsy showed only chronic cervicitis. So in 30 cases there were 5 false positives (1.67%).

False Negative.—Table 3 shows the details of 6 false negative cases. In case 1, no clinical diagnosis was reached and was labelled as a case of bleeding per vagina. Cytologically there were no malignant cells. Histology showed a hydatiform mole of early malignancy. In case 2,

TABLE 3.—*False Negative Cytology. (Cases with Negative Cytology and Positive Pathology in* 300 *Patients*).

Clinical Diagnosis.	Smear Diagnosis.	Pathology.
1. Bleeding per vagina.	No malignancy.	Hydatiform Mole. (Early malignancy).
2. Cancer Cervix	No malignancy	Carcinoma in Situ.
3. Cancer Cervix	No malignancy.	Epidermoid Carcinoma insufficient for grading.
4. Malignant Tuberculous Cervix	No malignancy	Carcinoma in Situ.
5. Chorion Epithelioma?	No malignancy (Twice)	Chorio-Carcinoma.
6. Chorion Epithelioma	No malignancy	Chorio-Carcinoma.

which was clinically cancer of the cervix, no malignant cells were detected, but histology showed carcinoma *in situ*. In the third case the epidermoid carcinoma was insufficient for grading. In case 4, the clinical diagnosis of malignancy was not certain. Cytology did not reveal malignant cells, but on histology, carcinoma *in situ* was detected. In cases 5 and 6, the clinical diagnosis was chorion epithelioma, but cytology did not reveal malignant cells. Histologically they were cases of chorio-carcinoma. Thus these cases comprised of chorionic carcinoma or early epidermoid carcinoma of the cervix. In 300 cases there were 6 false negatives (2%).

COMMENTS

Our figures are in accordance with those of Meigs and co-workers[2],[3],[4] and others who after Papanicolaou[5] did a thorough investigation of the test. They[3] published the report of 220 cases with an error of 2.2 per cent in cervical cancer and 8.3 per cent in endometrial cancer. Their false positives were 2.6 per cent. Later in 1945, Meigs and others[4] published a complete report of 1,015 cases with an error of 4 per cent. Again in 1947, Meigs[2] reported a 3.2 per cent error in 2,749 cases. In 1948, Scheffey, Rakoff and Hoffman[7] reported 500 cases of cancer of the uterus and cervix and obtained 94.8 per cent correct results and 5.2 per cent incorrect results, 7 false positives and 19 false negatives out of a total of 500 cases. In 1948, Mackenzie, Watchler, DuBois and Neustaedter[1] reported 90 per cent correct results in malignancy. In 1949, Papanicolaou[5] emphasized the excellent results obtained after statistical evaluation of 3,195 cases. The results showed no false negative and one false positive (0.03%).

It has been urged by those who have done the most work on smears that the diagnosis from the smear should not be taken as final. The reason for this has never been closely brought out, and for this reason the warning has not received the attention it should. From the reports of Papanicolaou, Meigs and others, the accuracy of the diagnosis on the smears is as good if not better than the accuracy of diagnosis from a biopsy specimen. If these figures truly represent the method, it is difficult to understand why it cannot replace the biopsy. From our experience it seems obvious that error in diagnosis by the smear technic is confined to a small group of patients.

It is admitted by all who have used the method that diagnosis demands a great deal of time and experience. The method has not as yet become a practical laboratory procedure for general use. We feel that the method should have continued study in a large group of cases.

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Wife : " Doctor, I want the truth. Is there no hope for my husband?"

Doctor : " Madam, I'm afraid that he can't recover, but to make sure, I'm going to call in another doctor."

* * *

Rokitansky of Vienna, well known for his contributions to pathologic anatomy, was married to a highly gifted singer. They had four sons of whom two became physicians and two singers. When someone asked the father about his sons, his laconic reply was : "Two heal—two howl!"

A man walking along the street, carrying a couch on his back, was stopped by a policeman.

" What goes on here?" the policeman asked.

" Nothing much," the man replied, " I am a psychiatrist going on a home call.'

From Tonics and Sedatives, J.A.M.A. 147 : 8, 1951.

* * *

Some months ago an escaped mental hospital patient decided to impersonate a member from the State of............As such, he addressed the.......House and ....on April 11th last, and on the same day attended and advised a meeting of the........Taxation Committee. He was finally identified as one Paul Snow of ....His remarks were said to have deeply stirred the good legislators, who enthusiastically adopted some of the novel proposals which he presented with such clarity and close reasoning.

Now comes a comment on the affair from the editorial of Medical Times. " May this episode not, as a matter of fact, represent a frequent occurrence? Do not the weird performances of our legislators, suggest that participation of mental hospital " delegates " happens oftener than has hitherto been realised? The inference seems inescapable."

—From " This busy world and I......," Medical World, 75 : 156, 1951.

ORIGINAL ARTICLE

CYTOLOGIC DIAGNOSIS OF PROSTATIC CARCINOMA †

P. N. Wahi *

Recent reports on the application of the smear method of cytologic diagnosis of malignancy, to carcinoma of the prostate, appeared promising, and offers a diagnostic procedure applicable at a stage when the condition is not already inoperable. Such a test, if reliable, might be employed as a routine measure in the examination of men in the cancer age group, with a consequent reduction in the high mortality of prostatic carcinoma.

The present methods of diagnosis are obviously reflective. Rich [18] has reported that in 292 consequent autopsies in men over 50 years, at the Johns Hopkins Hospital, 14 per cent showed carcinoma of the prostate and that in 65 per cent of these, a diagnosis of carcinoma was not made during the life time of the patient. Carcinoma of the prostate is diagnosed by clinical, histologic or biochemical methods. A low percentage of patients are expected to benefit by the treatment when the disease is recognisable by rectal palpation. Digital examination of the prostate may give information from only a limited area of the prostate. Biopsies are useful when suspicious areas are present in the palpable portion of the gland. Most authorities agree that the attempt to obtain tissue for histological examination by punch biopsy, transurethral resection or by perineal exposure is frequently met with failure. It is more so in the early stages of the disease when the urethral portion of the gland seldom contains a carcinoma.

Studies undertaken to evaluate exfoliative cytology in the diagnosis of prostatic carcinoma are justified because of the present inadequate methods of biopsy and the inaccuracy of the clinical diagnosis. It is hoped that this method may permit an earlier diagnosis to be made. The secretion collected by massage will make available for study, cells from all parts of the gland connected to the urethra by patent ducts. This method is promising because it is not troublesome to the physician or the patient and can be employed by doctors in charge of smaller hospitals for whom biopsy may be impossible. Further, they need not read the smears themselves but can always send them, after fixation, to experts. Such a test, if ultimately proved to be reliable, can therefore be used as a routine measure to check the possible existence of prostatic carcinoma in men of that age group.

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† Paper read at the Annual Conference of the Association of Pathologists of India, at Hyderabad, in November, 1951.

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REVIEW OF LITERATURE

Review of literature failed to disclose any mention of a study of malignant cells in the prostatic secretion previous to the report, in 1931, by Mulholland[11]. He studied a series of patients who were not suspected of having a malignant disease and another series of patients with clinically malignant lesions of the prostate. He observed abnormal cells in 77 per cent of the second group but refrained from calling them carcinoma cells.

Papanicolaou and Marshall,[13] Papanicolaou[14], [15], and Daut[4] have reported cells of prostatic carcinoma in urine. Papanicolaou[14], in 9 cases of carcinoma of the prostate, examined urine specimens in the course of estrogenic treatment with or without previous orchidectomy. In all but one case, definite cancer cells were found in the smears. In some instances the cells were small, had a dense nucleus and appeared in a relatively small number. In others they were numerous, appearing in large clusters, and showed definite activation of their nuclei and anisocytosis. Some cells displayed strikingly aberrant forms and looked like cancer cells enlarged beyond normal limits and remodelled by the prolonged estrogenic therapy. Other workers[3],[5],[7],[9] studied sediment from the urine voided after prostatic massage.

Herbut and Lubin[7], in 1947, published the second article to appear in the literature dealing with malignant cells in the prostatic secretion. They used the Papanicolaou[12] technic of staining and obtained the specimens by the standard method of prostatic massage. Prostatic secretions from 100 patients were examined, and a diagnosis of carcinoma of the prostate was rendered 17 times. The diagnosis was confirmed histologically in 10 of these cases. In only one case was the diagnosis made when the disease was not evident clinically, but in this case the diagnosis was not proved histologically. These authors set forth two criteria for the diagnosis of carcinoma from the examination of prostatic secretions: (1) the presence of an unusual number of multi-coloured pavement cells and (2) the presence of cancer cells.

Albers, McDonald and Thompson[1] examined 41 cases of clinically malignant prostates. Secretions were obtained in 24 of these and tumour cells were present in 13. In these the diagnosis was confirmed histologically. In addition they found 3 cases of carcinoma out of 100 cases of clinically benign hyperplasia in whom the diagnosis was proved by transurethral resection. Herrold[8] stained the smears with Wright's stain and also by the Papanicolaou technic and compared the two to determine whether the smears stained by Wright's method may serve as a useful ' screening ' process to rule out the necessity of the Papanicolaou method for lesions which on digital palpation impress one as being more inflammatory than malignant. He preferred to collect the prostatic secretions in a container ; then after thorough shaking the smears were made which, therefore, represented a sample of the secretions of the whole gland. Herbut[6] in 1949 published his results of 520 preparations from a total of approximately 480 patients. In this series, 66 patients had histologically or clinically proved carcinoma of the prostate and he found neoplastic cells in 54 (81.8%) of these.

Boyer[2], in 1950, studied smears from 198 men, 44 of whom had known and 17 clinically suspected malignancies. He had a high percentage of false negative reports among the known positive cases, and failed to detect malignancy in the suspected cases and among 97 men in the cancer age group. With these findings he was forced to conclude that frequent careful rectal examination of men over 45 years of age and more frequent and an earlier use of the perineal biopsy remain the principal armamentaria against carcinoma of the prostate. Hock, Wood and Kosinski[9] studied prostatic smears in 150 cases in an attempt to correlate the presence of malignant cells with the existence of very early and clinically undetectable carcinoma of the prostate and to evaluate the routine use on this procedure in males past 50 years of age. Out of the 13 cases with cancer proved clinically by biopsy, 4 were positive and 4 were suspicious on smear examination, making a total of 8 (61.4%). Peters[16], in the same year, described in detail the cells found in the prostatic smear. The cellular elements in the stained smear in the physiological and pathological states of the prostate were described. Johnson and Fajers[10] reported the results of investigating the prostatic secretion in 110 patients. They were able to diagnose 16 cases of cancer with certainty and a suspicion of cancer in 11 cases, 5 of which were verified as cancer.

Peters and Young[17], in 1951, reported the findings of smear examinations in 162 patients. Forty-four cases of this series had clinically or histologically proved carcinoma. In 38 of these 44 cases, malignant cells were present in smears, 4 were suspicious of cancer, while 2 cases were false negative. Out of 102 patients with benign prostatic lesions one case was false positive.

METHODS AND MATERIALS

Technic of Making Smears and Fixing.—The prostatic secretions were obtained by prostatic massage. Proper massage is essential to obtain adequate secretion for cytological study. As much as possible of the seminal vesicles and ampullae should be avoided. The whole gland should be massaged, beginning at the borders and massaging towards the urethra several times with gentle pressure. Finally, the secretions should be expressed into the urethra by massage of the median groove from base to apex. The drops of secretion appearing at the external urethral meatus are collected on clean new glass slides. Each drop is then covered with another clean slide and compressed. This allows the fluid to spread evenly over the surfaces. The top slide is pulled off longitudinally under moderate pressure resulting in two smears, usually one cell in thickness. The smears should be uniform. While the smears are still wet they are put into a mixture of equal parts of 95 per cent alcohol and ether in which they are allowed to fix for a minimum of fifteen minutes. Four smears are routinely made. If for some reason, staining cannot be carried out immediately or if the slides have to be sent by mail, the smears are removed after fixing them for the required time and allowed to dry at room temperature. The glycerine mailing technic may also be employed. The slides are stained by the Papanicolaou technic. The preparation of the staining solutions and the staining technic has been previously described in detail[20].

In order to become familiar with the various normal and abnormal cells, impression smears from normal, hypertrophied and malignant prostates were prepared and studied. The smears are prepared by squeezing bits of fresh tissue with forceps, expressing fluid on to slides for pull-smears. In some cases, because of the paucity of tissue fluid, it is necessary to make direct smears by pressing the tissue against the slides and rubbing it as needed. After preparation of smears, the slides while still wet are fixed in an ether-alcohol mixture and stained in the usual way.

This investigation embodies the result of 52 cases of enlarged prostate admitted to the S. N. Hospital, Agra. Studies were also conducted on smears of normal cases in the cancer age group. The purpose of the study is (1) to become familiar with the cytologic characteristics of normal prostatic secretions, (2) to study the cytological changes found in prostatic secretions of malignant cases, (3) to become familiar with the normal and abnormal cells by study of the impression smears and (4) to attempt the diagnosis of prostatic carcinoma by the examination of smears obtained after the prostate massage.

CYTOLOGICAL FINDINGS

Non-Neoplastic Cells :—The following cells and elements may be found in the normal prostatic secretions :

1. Epithelial cells (*a*) Squamous
   (*b*) Columnar
2. Inflammatory cells *e. g.* Neutrophils, lymphocytes, plasma cells and histiocytes.
3. Spermatozoa
4. Corpora amylacea
5. Bacteria
6. Lecithin and lipoid bodies.

Squamous Epithelial Cells (Fig. 1) : These are the urethral cells and are easy to identify. These are the usual large flat pavement cells as seen in urinary sediment or vaginal smears. They are seen singly or in clusters and are larger, polyhedral, round, oval or irregular cells. There is abundant homogenous cytoplasm, pale blue to greenish grey or sometimes pink or orange in colour. The outer contours are sharp but they may be folded, wrinkled or partially rolled up. They have small, dark, round or oval and usually central nuclei. The younger cells are with larger nuclei and proportionately less cytoplasm.

Columnar Epithelial Cells (Fig. 2, 3) : The cells from the acini, seminal vesicles, ejaculatory ducts, smaller accessory glands and the urethral mucosa show the same general pattern on the smears.

The columnar cells are present singly or in small groups of 3 or 4 cells. They are relatively small, being 10 to 15 microns in diameter. They are cylindrical, rounded, or oblong in shape and their borders are sharp. There is a moderate amount of cytoplasm, homogeneous, and light green or bluish green in colour. The nuclei are half to one third the size of the cell and are round or oval and of uniform size. Their borders are sharp and chromatin is clumped in minute granules. Nucleoli may be absent or small. In groups, the cells are irregularly arranged or present in loose cluster or mosaic-like pattern. The non-malignant groups show cells of uniform size, nuclei of uniform shape and size with uniform distribution of chromatin and equal spacing of cells with intact borders.

Sometimes, degenerated cells are present which show rounded but distinct borders, foamy, reticulated or vacuolated cytoplasm and rounded or elongated eccentric nuclei. These are usually two to four times the normal size.

Epithelial cells from the seminal vesicles (Figs. 4, 5) can be easily recognised as a definite entity. These are three to four times the size of prostatic cells, are round in shape, and occur singly. The nucleus is usually eccentric and the cytoplasm is bluish green and contains brown pigment granules. Smears with a large number of such cells also contain large numbers of spermatozoa. However, it might be noted that once these cells become malignant it is difficult to distinguish them from malignant prostatic cells.

Inflammatory Cells (Fig. 6) :—These comprise neutrophils, lymphocytes and plasma cells and are easily recognised.

Histiocytes (Fig. 7) :—These may closely resemble columnar cells. They are present singly or in clusters and are slightly larger than the columnar cells. When in clusters, they may resemble giant cells. The nuclei are larger than those of columnar cells and nucleoli are fairly frequently seen. The cytoplasm is abundant and may show vacuolation or cellular inclusions. The cellular inclusions consist of cellular debris, leukocytes, erythrocytes, pigment granules, dead spermatozoa, *etc.* These are helpful in their diagnosis.

Spermatozoa (Fig. 8) :—The spermatozoa are readily identified when alone but may be found inside the histiocytes.

Copora Amylacea (Fig. 9) :—These are occasionally seen as pink homogenous masses with no organised internal structure. These vary in size and shape.

Bacteria and Lecithin Granules :—They appear on these smears just as in other preparations. Lecithin bodies form a granular background for the smears. In infected cases they are noticeably decreased in number.

SECRETIONS IN BENIGN PROSTATIC HYPERTROPHY

In benign prostatic hypertrophy there is a moderate increase in the number of columnar cells. They are like those found in normal prostates, but are slightly larger. This is due to an increase in cytoplasm. The cell margins are distinct and polyhedral. They are present in groups of usually not more than half a dozen cells. Nuclei are small, round or oval. Nucleoli are more frequently seen and more easily recognised (Fig. 10, 11, 12).

NEOPLASTIC SECRETIONS

There is no absolute single criterion for making a positive diagnosis, but various factors must be evaluated. The malignant characteristics may be considered from the stand point of the individual cell and from that of clusters of cells. In clusters of cells, the hyperchromatism and indistinctness of cellular outline are more marked, due to the proximity of the cells.

Changes in the character of the nucleus are of greater diagnostic significance than alteration in the size and form of the cells or cytoplasmic changes.

There is a greater relative increase in the size of the nuclei than of the cytoplasm resulting in a high nuclear-cytoplasmic ratio. The variation in the size of the nuclei is not much marked but an increase in the size as compared to that of the nuclei in normal cells is important. The nuclei are round, oval or elongated and occupy half or more of the cell. Abnormal nuclei are more prominent and frequently take a darker stain. Nuclear chromatin shows coarse granularity, sometimes amounting to heavy clumping. The nucleoli are often prominent and large, resulting in a change of the nuclear-nucleolar ratio. The presence of multiple nucleoli is significant. The mitotic figures may be present but are not frequent.

The malignant cells are usually larger than normal columnar epithelial cells. The normal columnar cell is 1 to 2 times the leukocyte while the malignant cell is 4 to 5 times the leukocyte. The cells are round

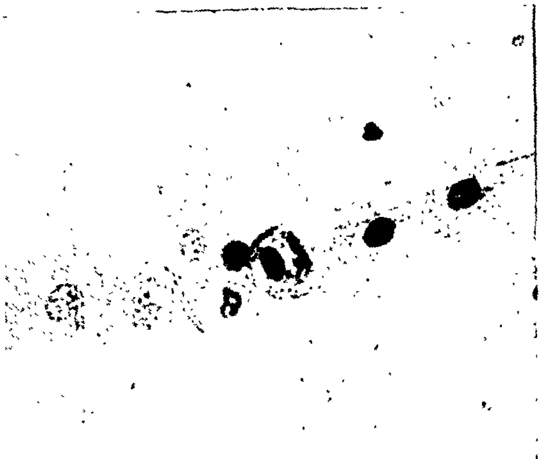


Fig. 1.

Fig. 1.—Squamous epithelial cells in prostatic secretion. These are the usual large flat pavement cells as seen in urinary sediment. X 430.

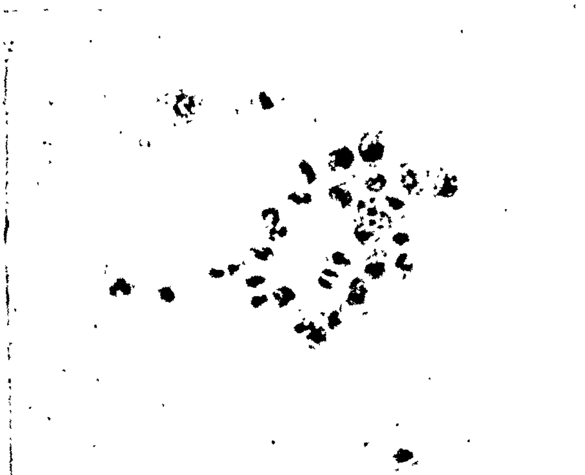


Fig. 2.

Fig. 2.—Normal columnar epithelial cells in prostatic secretion. The cells are of uniform size and the nuclei of uniform shape and size with uniform distribution of chromatin. The cell borders are clearly defined. X 430

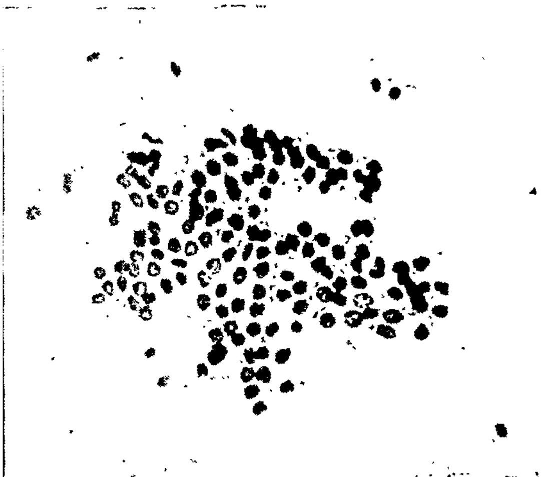


Fig. 3.

Fig. 3.—Normal columnar epithelial cells in impression smear of prostate. Note uniformity of cell size, shape and spacing with intact borders. X 430

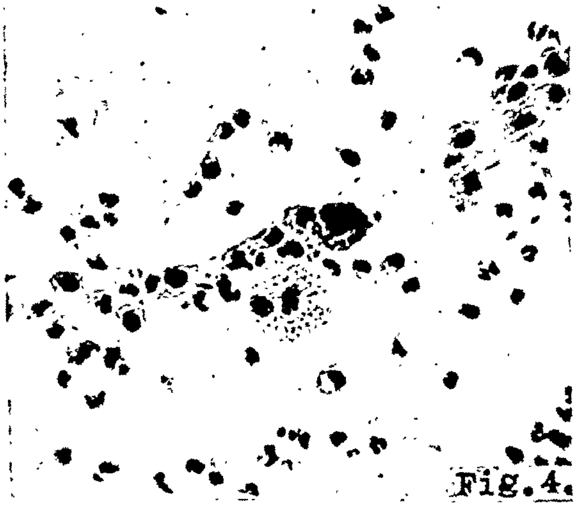


Fig. 4.

Fig. 4.—Normal epithelial cells from seminal vesicles. These are three to four times the size of prostatic cells, are round in shape and occur singly. The nucleus is usually eccentric and the cytoplasm contains brownish pigment. X 430

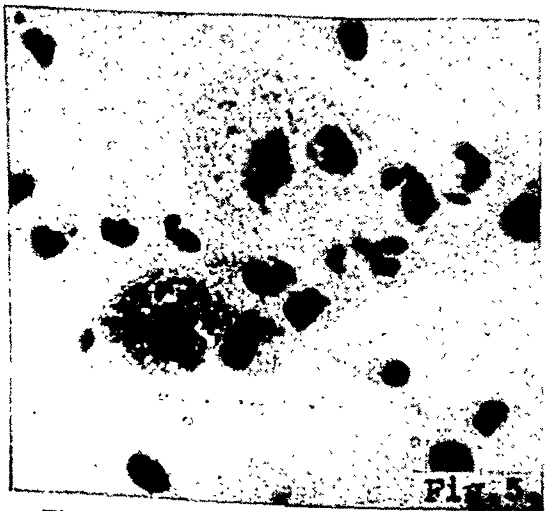


Fig. 5.

Fig. 5.—Normal epithelial cells from seminal

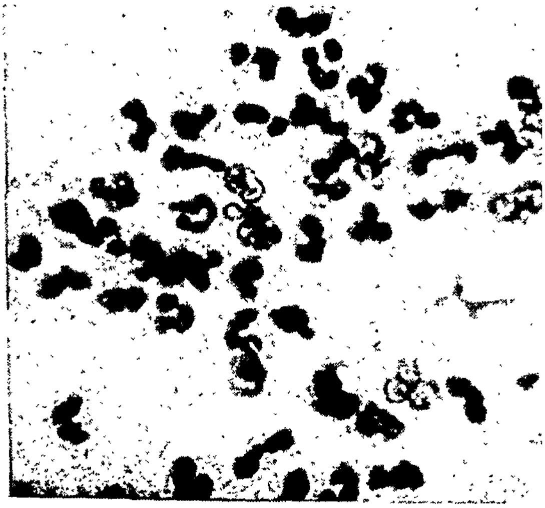


Fig. 6.—Inflammatory cells in prostatic

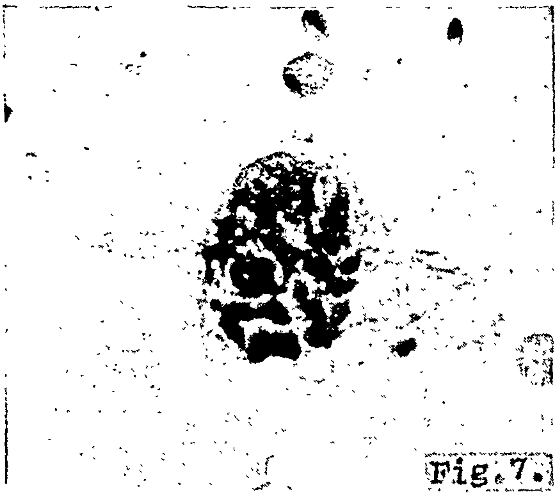


Fig.7.

Fig. 7.—Histiocyte in a normal prostatic smear showing abundant vacuolated cytoplasm and cellular inclusions, which are mostly dead spermatozoae. X 970

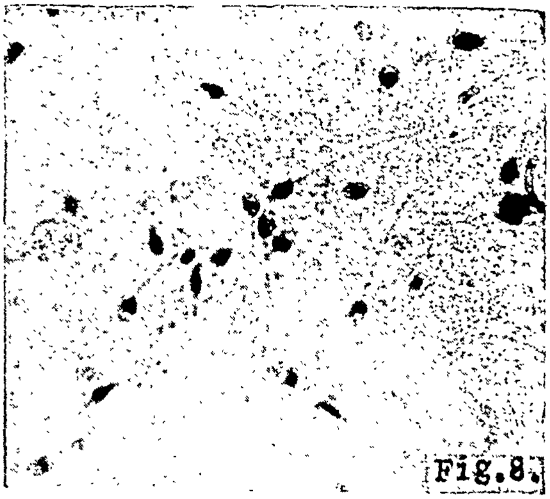


Fig.8.

Fig. 8.—Spermatozoa in a normal prostatic smear. X 970

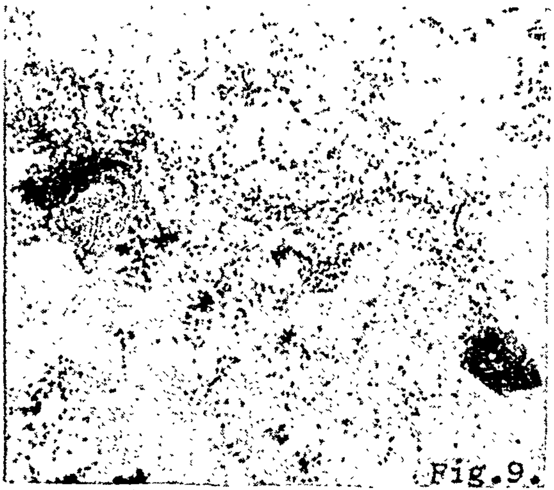


Fig.9.

Fig. 9.—Corpora amylacea in a normal prostatic smear appearing as pink homogenous masses without any organised internal structure, and varying in shape and size. X 430

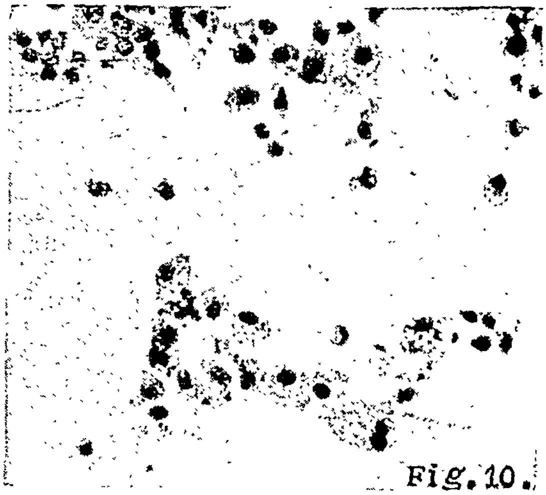


Fig.10.

Fig. 10.—Columnar epithelial cells in prostatic smear of a case of benign hyperplasia. Note the slightly larger size of the cells which is due to increase in cytoplasm. The cell margins are distinct. X 430

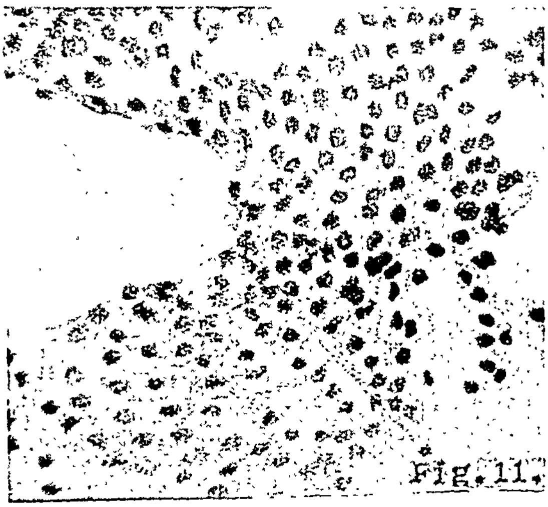


Fig.11.

Fig. 11.—Columnar epithelial cells in impression smear of prostate showing benign hyperplasia. (Same case as fig. 10). Increase in cell size is well noticed. This is due to increase in cytoplasm.

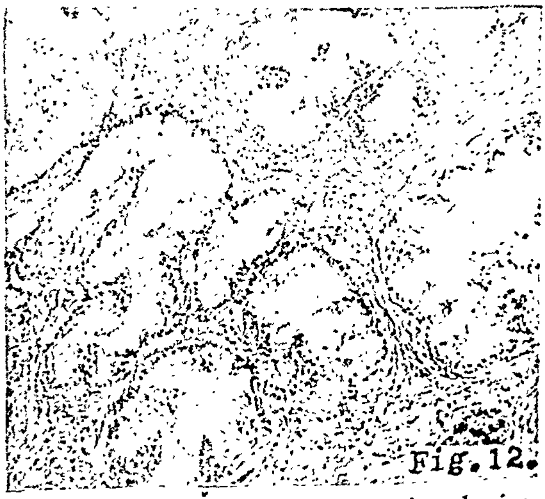


Fig.12.

Fig. 12.—Photomicrograph showing benign hyperplasia of prostate. (Same case as figure 10). X430.

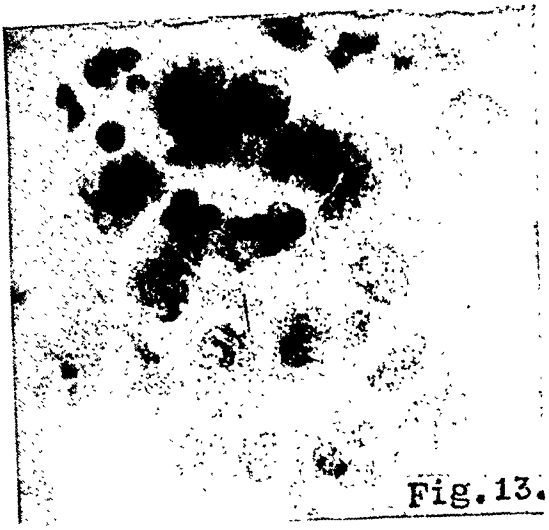


Fig. 13.

Fig. 13.—A clump of cancer cells showing increase in size, hyperchromatism of nuclei and lack cytoplasmic detail. X 970

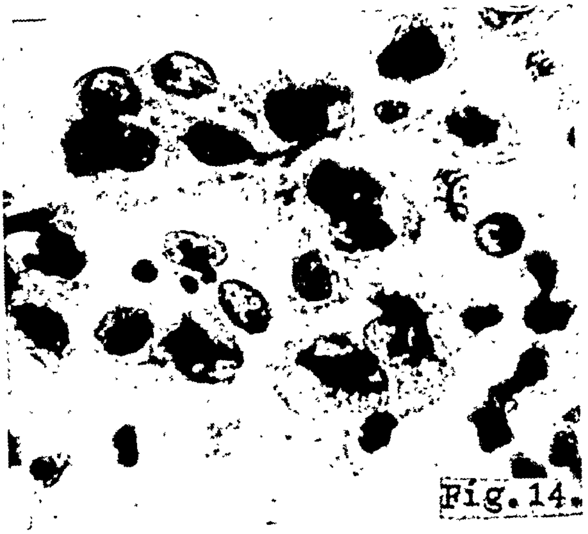


Fig. 14.

Fig. 14.—A group of malignant neoplastic cells showing large hyperchromatic nuclei with ill-defined cytoplasm and absence of clear cell boundaries. X 970

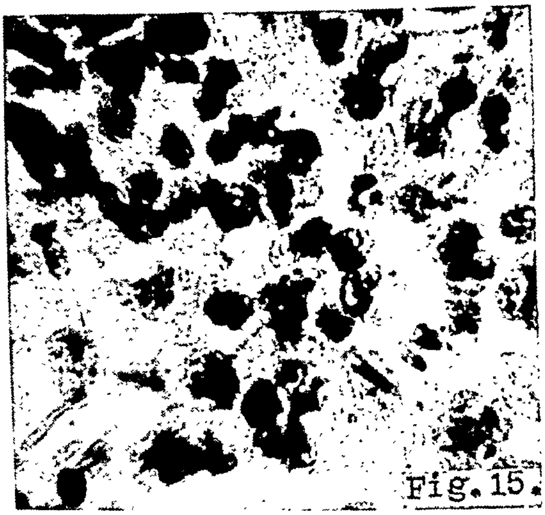


Fig. 15.

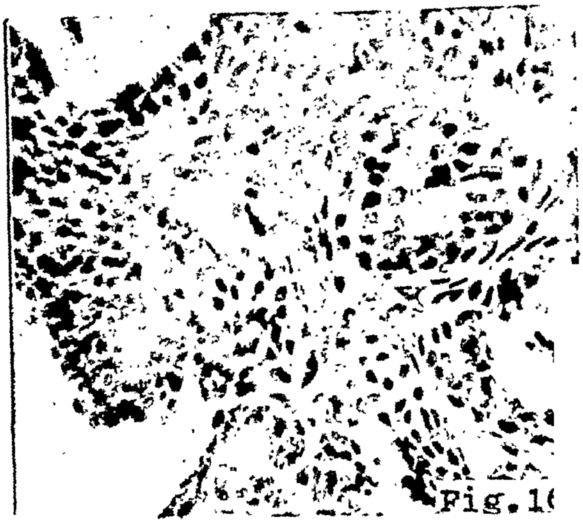


Fig. 1

Figs. 15, 16.—Massage specimen and tissue section from same man showing malignant cells in smea and adenocarcinoma histologically. X 970 and X 430

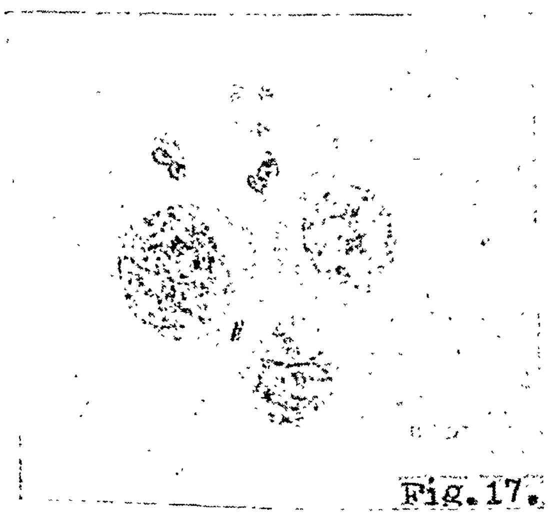


Fig. 17.

Fig. 17.—Malignant cells in massage smear of prostatic cancer. X 970

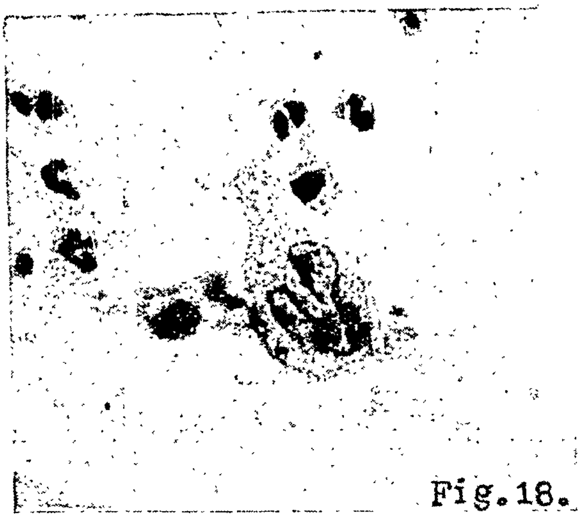


Fig. 18.

Fig. 18.—Single malignant neoplastic cells in massage smear of carcinoma of prostate. X 970

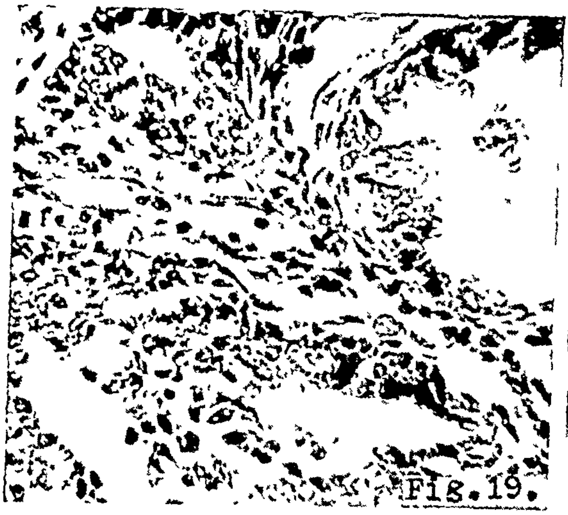


Fig. 19

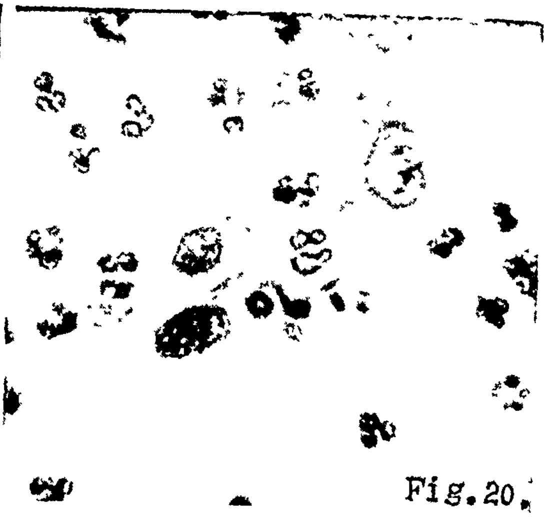


Fig. 20

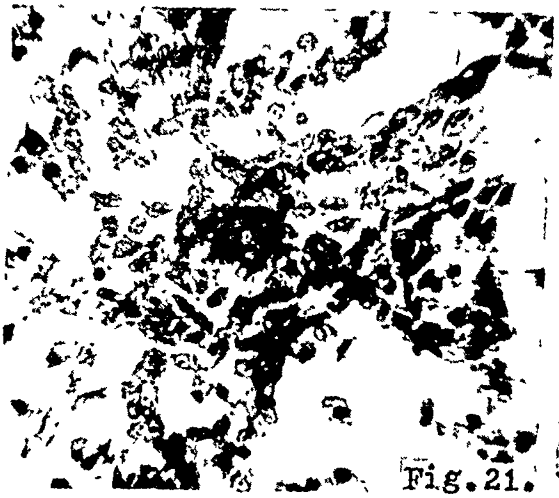


Fig. 21

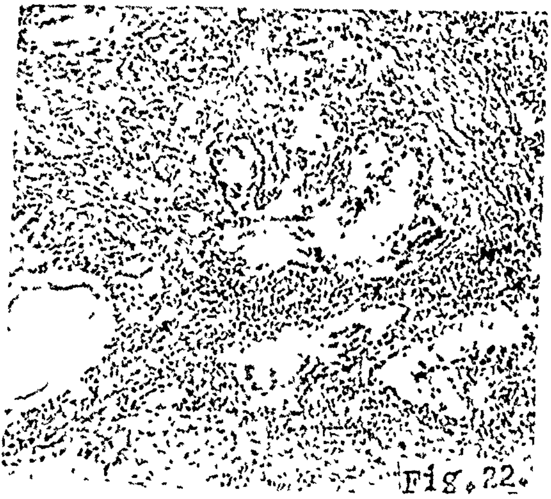


Fig. 22

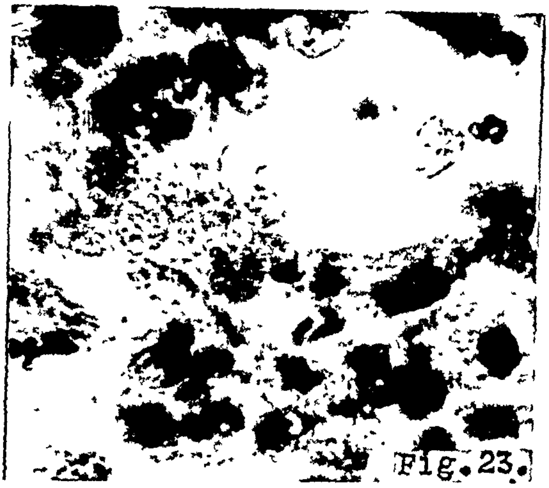


Fig. 23

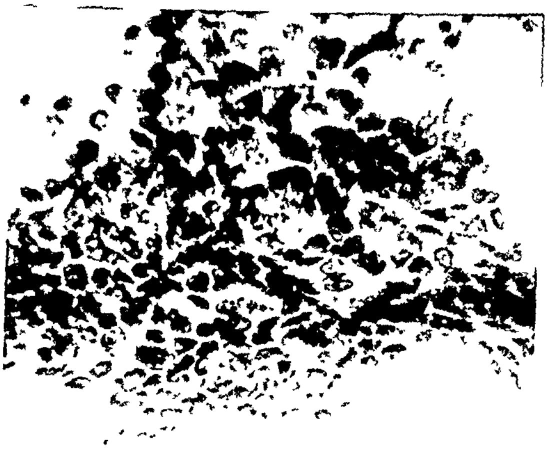
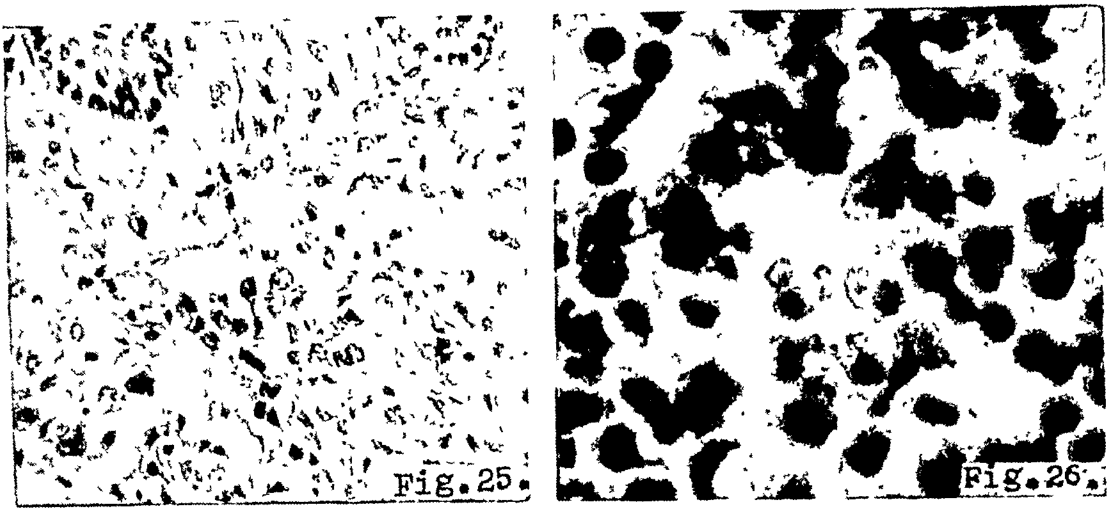


Fig. 24

Figs. 19, 20, 21.—Tissue section, massage smear and impression smear from a case of prostatic carcinoma. The tissue section (fig. 19) shows an early adenocarcinoma. The massage specimen (fig. 20) shows individual malignant cells showing relatively large nuclei, hyperchromatism and prominent nucleoli. The impression smear (fig. 21) shows marked nuclear hyperchromatism, crowding of cells and loss of cytoplasmic definition. X 430, X 970, X 970.

Figs. 22, 23, 24.—Tissue section, massage smear and impression from one individual—a case of carcinoma of prostate. Changes described above are characteristically seen. X 100, X 970, X 430.



Figs. 25, 26.—Tissue section and massage specimen of a case of adenocarcinoma of prostate. X 430, X 970.

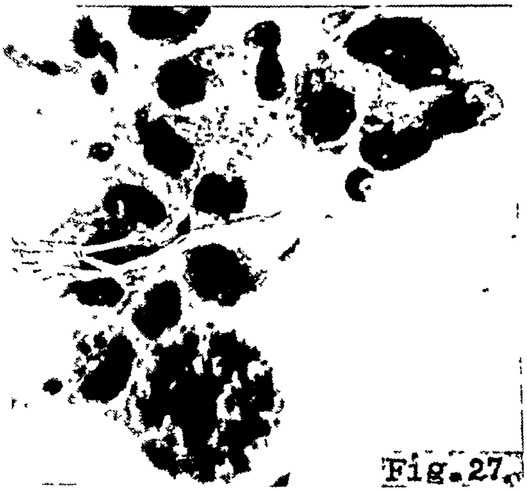


Fig. 27.—Prostatic massage specimen from a case of carcinoma showing hyperchromatic nuclei, dense nuclear membranes, prominent nucleoli and loss of cytoplasmic definition. A large cell, probably histiocyte with marked cellular inclusions can be seen. X 970

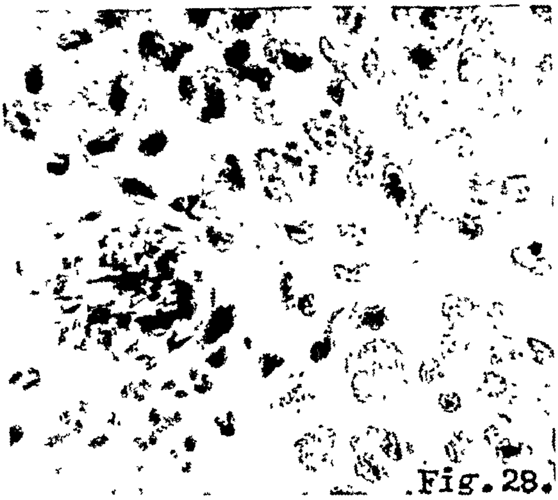


Fig. 28.—Massage smear from a case of prostatic carcinoma showing cancer cells, histiocytes, inflammatory cells and spermatozoae. X 970

or oval but variation in size is commonly marked. The cytoplasm is considerably reduced and the cell borders are indistinct. Pleomorphism is a relatively unusual finding, most of the cells retaining a round to oval shape. Cytoplasm stains pale bluish green to light yellow or orange in colour. When cells are present in clusters, the borders of masses of cells are irregular, frayed and indistinct. Cytoplasm forms a syncitial mass. There is thus a loss of cellular individuality (Figs. 13-28).

RESULTS

In this study, till date, 52 cases of pathological prostates were examined. In this group there were 15 patients with carcinoma of the prostate in whom a diagnosis was proved by paraffin section in 12 and was certain clinically in 3.

Cancer cells were found in 13 of these 15 cases (86.6%)—Table 1. This result is in conformity with the finding of 81.8 per cent positive by Herbut.[6]

TABLE 1.—*Results in 15 Cases with Proved Prostatic Cancer.*

Total number of patients with cancer proved by biopsy or clinically	15
Number of positive preparations	12
Number of suspicious preparations	1
Number of negative preparations	2

Of these 15 cases, 6 were diagnosed clinically as definite or suspicious of malignancy. The following table (Table 2) gives the cytological diagnosis in these cases.

TABLE 2.—*Cytological Diagnosis.*

Clinical Diagnosis	Cytological Diagnosis.			
	Number.	Positive.	Negative.	Suspicious
Carcinoma (proved)	4	3	1	0
Suspicious of carcinoma	2	2	0	0

The one which was false-negative also had a negative biopsy but was proved to be adeno-carcinoma on histological examination of tissue removed after operation. There were no false positives.

There were 2 patients whose prostatic secretions were negative cytologically. In one, a clinical diagnosis of carcinoma was definite and in the other, the diagnosis was enlarged prostate,—malignant? It is in this group of patients with a negative cytologic diagnosis that one cannot definitely rule out malignancy. Biopsy proved both these cases to be malignant. It is, therefore, important that in cases of definite clinical malignancy; if a smear is negative, the diagnosis should be confirmed by biopsy.

A clinical diagnosis was made in 6 of 15 cases (40%) of malignancy, proved by smear or histologically. This shows that 60 per cent of cases were missed clinically. This is in conformity with Rich's[18] report where 65 per cent of cases have been missed clinically. By an additional adoption of the smear method 88.6 per cent were detected as malignant. This shows that the cytologic diagnosis of carcinoma of the prostate has a very important role to play in the routine detection of carcinoma of the prostate in the cancer age group of patients and if applied at an early stage, radical prostatectomy may be usefully employed.

DISCUSSION

No definite conclusions can be reached from this study of the relatively small number of cases comprising it. However, as this method of diagnosis of prostatic carcinoma has not received enough attention as compared to its wide use in the diagnosis of cervical carcinoma, it is considered that the presentation of this series may make a useful contribution.

The majority of workers reported a significant percentage of positive results. Mulholand[11] found suggestive abnormal cells in 77 per cent of 30 cases examined by smear method. Herbut and Lubin[7] reported the finding of malignant cells in 89 per cent of cases. Herbut[6] detected neoplastic cells in 54 of the 66 patients (81.8%). Hock, Wood and Kosinski[9] found a 61.4 per cent correlation of positive smears to prostatic carcinomas. Boyer[2] reported a rather low percentage (36.3%). Most of the in-patients in the malignant group were under estrogen therapy at the time of examination and they think it might be the cause of the poor results.

From the results, it is clear that the recognition of malignant cells in the prostatic secretion is feasible, but a careful preparation and a thorough examination of the smears is essential. Difficulty in obtaining a good smear after a successful massage has been real, mostly due to a tender and indurated prostate caused by an advanced state of cancer. When the clinical diagnosis does not coincide with prostatic smear finding, the smear should be repeated at least twice before a definite positive or negative result is given. A positive cytologic diagnosis would be of great value in clinically uncertain cases. A negative result does not rule out carcinoma.

It is the experience of most surgeons and pathologists that the attempt to obtain tissue for histologic examination by punch biopsy, transurethral resection or perineal exposure is frequently met with failure. This is essentially so in early cases where it is often not possible to obtain the tissue from the correct place. It is still more difficult when the gland is normal to palpation. In five clinically malignant cases (definite and suspicious), biopsy was positive for malignancy in only one; in the remaining 4 cases only fibrous tissue was seen. Prostatic smears were positive in 4 cases. In 2 of 5 cases where operation was performed, both showed adenocarcinomata on histological examination of the operated tissue. One of the cases is reported in more detail as the biopsy was negative twice and yet malignant cells were present in the secretion.

CASE REPORT

C., aged 75, was admitted with retention of urine for 3 days. He also gave a past history of retention of urine. Rectal examination showed a hard, enlarged prostate with a suspicion of malignancy. Biopsy material revealed only fibrous tissue. A prostatic smear was made and stained by the Papanicolaou technic. Malignant cells were seen. The surgeon was hesitant to perform a radical prostatectomy on the basis of the smear report alone. He repeated the biopsy and again the tissue obtained was negative for malignancy. The second smear was also prepared. It was again positive for malignant cells. The surgeon removed the prostate and histologically an adenocarcinoma with low grade malignancy was found.

The next problem at this stage of the present investigation is to find out whether the presence of malignant cells in the smear of prostatic secretion from prostates, which are clinically either apparently normal or suspicious, is sufficient evidence to warrant a radical prostatectomy. With our limited experience coupled with the reports of other workers, it can be justifiably concluded, that if cancer cells are present on two repeated examinations, then even if the prostate is clinically negative, this should be taken as a positive evidence of prostatic malignancy. In cases where the prostate is clinically suspicious then positive smears are still stronger proof ; while in cases where the smears are negative a biopsy should be done before advising radical surgery. However, it must be remembered that a negative report from either or both does not rule out carcinoma. It is a safe rule to perform repeated smear examinations in cases where the clinical and cytological diagnosis do not agree, before giving a definite opinion on the smear.

SUMMARY AND CONCLUSIONS

From the results of this investigation it can be concluded that it is definitely possible to recognise the presence of malignant cells in smear of the secretions obtained by prostatic massage and fixed and stained by the Papanicolaou method.

The description of normal cellular elements found in prostatic secretions together with the diagnostic criteria for malignant cells is presented.

The examination of prostatic secretions of malignant cells is of greater value in the diagnosis of clinically uncertain and early carcinoma.

One case has been cited to show that it was on the basis of the smear report, inspite of a twice negative biopsy, that the surgeon performed the radical resection. The action was justified by the finding of malignancy in the operated material.

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SOME OBSERVATIONS ON THE BEHAVIOUR OF THE WASSERMAN AND KAHN TESTS (S. T. S.) IN LEPROSY AND TUBERCULOSIS. †

P. G. Gollerkeri[1], B. B. Gokhale[2], and S. N. Ranade[3]. *

Leprosy is an infection causing obvious lesions of the skin, specially sometimes on the exposed surfaces of the body, like the face, hands and feet. To the unwary these skin lesions, at any rate in their early stages, are not seriously significant, and some local medication is resorted to, with the mistaken diagnosis of a fungus or other skin disease. It is usually in the skin clinic of a large General Hospital that leprosy is soon recognized and handled separately from other skin diseases.

The other well known common infections involving the skin with obvious lesions in it, of one or another kind and mistaken for what it is not, is syphilis in its secondary or later stages. There is thus much overlapping of diagnoses of leprosy, syphilis and the large number of parasitic and other skin infections.

Syphilis, the great imitator, has been found by experience to be the most amenable to an almost correct diagnosis by one or other of the serological test for syphilis (S. T. S.). In the course of a 'screening' investigation with S. T. S., a good many borderline cases crop up, with the S. T. S. reports equivocal, ranging all the way from 'strong positive', to " doubtful". Recognized anti-syphilitic treatment of these cases does not always succeed in the relief or amelioration of their skin or other symptoms. It is then, and sometimes even before the S. T. S., that a suspicion arises in the mind of the clinician that the lesions could be those of syphilis mixed with one or other active infection, *viz.*, leprosy or a fungal parasite.

Simultaneously, with the suspicion of a syphilitic infection in the systematic handling of these skin lesions, a bacteriological examination for *M. leprae* in the smears from the lesions, or wet preparations for fungus are carried out on the hospital case. The possibility of the co-existence of two or more infections simultaneously has to be thought of and investigated before any specific treatment can be started.

A good deal of literature has accumulated around the so-called " false positive " reactions of S. T. S. This euphemism presumably means that a subject not suffering from syphilis, gives a positive or near positive test for the disease. Such a conclusion follows upon the theory be reasoned out from another angle, even in syphilis. The pathognomonic cell *par excellence* in active syphilis is the well known and recognized plasma cell, derived from the lymphoid cell of chronic processes. The special chemical function attributed to this cell (the plasma cell derived from the lymphoid round cell) is due to its high lipoid content, a lipo-protease having a high affinity to the lipoid-rich parasite and cells[3]. The W. R. has been regarded as one of the means of detecting the presence of this specific antibody ferment in the serum. Early manifestations of syphilis in the skin and mucosa are said to be to be due to their comparative richness of lipoids[9],[12],[3].

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Applying these ideas to infections like leprosy and tuberculosis, and their erratic behaviour when their sera are tested with S. T. S., we have in these infections, theoretically at least, conditions suitable for positive reactions. Both these are known for their acid-fastness in staining reaction by virtue of their having a relatively impermeable (to ordinary stains) lipoid envelope. Whether it is this lipoid of the organism itself, or an excess of its opposite number, a lipolytic antibody in the serum is a moot point in the production of the positive S. T. S. when they occur in these two diseases. Serum lipase variations have been studied in leprosy in its treatment with chaulmoogra and the sulphones. A high serum lipase content has been found favourable to the success of the combined treatment with these drugs[11].

The latest in the field of S. T. S. is the cardio-lipin test. Though it has not yet come into general use, this test is said to be equally erratic in its results when applied to leprosy. The reason for this is vaguely ascribed to the lipoid component of the antigen (as in the other S. T. S. antigens) against the lipoids and the lipases in the serum of the leprosy patient[5],[1],[7].

S. T. S. in leprosy have been studied in our country and impressive figures to show that certain types of the disease constantly produce some degree of the positive reaction. The lepromatous type, associated with the easy demonstration of the bacilli in the lesions, have given the largest percentage of positives, while the neural types produce the smallest number of positive reactions[1],[13]. This is also corroborated by foreign workers, specially in the United States at their National Leprosarium, Carville. In America, the Kahn and cardio-lipin tests have been exclusively used in the immunological assessment of the various clinical types of leprosy[4],[6],[7].

The reason why in neural leprosy the S. T. S. tends to be less positive, is possibly because of the route of the involvement of nerve tissue. It is supposed, that the primary infection of the periphery spreads centripetally to the deeper nerve centres, a neurotropic affinity, in preference to the local dermal affinity, as suggested by the lepromatous lesions of the latter. This preference for localisation in the nerve tissues probably that the usual complement fixation and precipitin tests with the well known non-specific antigens are generally specific for syphilis, if strongly positive, when tested on the untreated and fully established disease for the first time. One of the present writers (P. G. G.) in his twenty years' experience of the Wasserman Reaction (W.R.) and somewhat less of the Kahn test, has come across puzzling reactions among clinically non-syphilitic subjects. A variety of conditions including leprosy, malaria, kala-azar, and even some cases of normal pregnancy have produced reactions similar to those of syphilis in one or another of its clinical stages or in the course of its treatment.

POSSIBLE FACTORS FOR THE POSITIVE S. T. S. REACTIONS

(*a*) The globulins : It is common knowledge that in infections of any kind specially the subacute and chronic types caused by bacteria, protozoa, spirochaeta, the viruses, fungi, *etc.*, or even in metabolic and nutritional disorders, the resulting blood changes of anemia are connected with the loss of protein, either as cell proteins and/or albumin from the blood and tissues. Considering the proteins of the plasma, other than fibrinogen, the loss of albumin from the body is much more noticeable than the globulin, so that some alteration in their ratio in the serum in favour of globulin is the natural corollary. Anti-bodies in serum are described as specialised globulins with their easier diffusibility than albumin. Such a disturbance in the albumin/globulin ratio in favour of the globulins may be argued as a factor in the production of the " false positive " reactions of the S. T. S. Some of these globulins may not be unlike the specialised globulin anti-bodies of syphilis[14].

(*b*) Unlike the other antigen anti-body reactions, the reactions of the S. T. S. are thought to be dependent not merely on the production of the specific globulin (?) antibody, the so-called complement fixing antibody of the W. R., but by a subtle increase of the lipoids (demonstrable or otherwise) of the serum [14].

The role of lipoids in S.T.S. reactions is obscure. In the preparation of antigens for the various S.T. S., an important element is the sensitization of the antigen extracts by the addition of an alcoholic solution of cholesterol. The question naturally arises as to why cholesterol added to the heart extracts should raise their sensitivity. This question could well be posed side by side with the observation that in some of the positive S. T. S. there is a demonstrable rise in the blood lipoids, for instance, in some cases of normal pregnancy[10].

A possible explanation could be, that a lipoid excess for one or another reason in the blood makes for the development of a corresponding antibody, a lipoid specific antibody, which adds up with the globulin antibody to give the positive reactions as in syphilis.

This lipoid factor for the development of the positive reactions can prevents the anti-substances from being produced or being mobilised into the blood stream for recognition in the S. T. S. It is a common observation that in tabes, general paresis, and the purely parenchymatous syphilis of the central nervous system, the S. T. S. of blood (and of cerebrospinal fluid) are notoriously equivocal. Parenchymal neuro-syphilis therefore compares well with neural leprosy in their behaviour in S. T. S. The reasons for this could be the same in both, whatever they are[13].

In a series of 285 cases of leprosy investigated by us with serological tests, Wasserman and/or Kahn, we recorded the following findings:

TABLE 1.—*Recordings of Tests in* 285 *Cases of Leprosy.*

Total No. Tested	S.T.S. Positive W.R. &/or Kahn	Per cent Positive.	Per cent Negative.	S.T.S. Negative.
285	71	24.9	75.1	214

TABLE 2.—*Smear Tests in* 71 *S. T. S. Positive Cases.*

Total S.T.S. Positive.	Smears for *M. leprae* Positive.	Bact. Positive (percentage).	Bact. Negative (percentage).
71	46	64.8	35.2

TABLE 3.—*Findings in* 46, *S. T. S. and Bacteria Positive Cases.*

Total of both S.T.S. & Bact. Positive	Lepromatous type.	Non-Lepromatous (Intermediate & Tuberculoid types.
46	26 (56.5%) 15 VD hist. 11 No VD hist.	20 (43.5%) 7 VD hist. 13 No VD hist.

Percentage of Positive S.T.S. & Positive for *M. leprae* in smears but with no history of venereal disease........24 in 46 or 52.5%

TABLE 4.—*Findings in* 214 *S. T. S. Negative Cases.*

Total S.T.S. Negative.	V.D. hist.	Lepromatous type.	*M. leprae* Positive.	*M. leprae* Negative.
214	25 (11.6%)	26 (12.1%)	39 (18.2%)	175 (81.85%)

From these tables it is fairly clear that a higher positive S. T. S. goes with a higher bacterial content made out from smears. Also, a lepromatous type in the active and progressive phases of the disease gives a higher positive S. T. S. We have already discussed that the lipoid rich bacilli and the lipoid rich tissue attacked could be factors in the development of the positive S. T. S[7]. The actual lipoid content in the lepromatous skin tissues has been estimated by special staining techniques by Jorge Campos. He has found that as high as 94 per cent of the 32 cases of lepromatous leprosy tested, gave positive lipoid reaction of the granulation tissue, while in the tuberculoid type, the percentage positive was 32, and in the undifferentiated, 53 per cent. Thus the thesis that positive S. T. S. can be ascribed, in part, at least, to the lipoid alterations in the serum, is probably sound. However, the bacteriologically positive cases and those which are clinically lepromatous with a negative S. T. S. tend to counter this supposition.

This inconsistency of the positive S. T. S. reaction and the corresponding laboratory findings of bacteriology, and the clinical one of the type of the disease, prevent any satisfactory deductions to be drawn from the reaction to infection, and how this reaction could be used in prognosis and treatment of the disease. Many of these positive S. T. S. cases of leprosy respond to the anti-leprosy treatment with a regression of the S. T. S. report to a clear negative, as also amelioration of their leprosy symptoms. While the usual anti-syphilitic treatment on the basis of the positive S. T. S. is of no avail either in the regression of the symptoms or of the S. T. S. positiveness. The original positive S.T. S. is thus solely due to the leprosy infection.

There appears to be some scope for the routine use of the lepromine test in the prognostic assessment of leprosy. From a few observations made by one of us (B.B.G.) this test compares well with the S.T.S. in that a positive S. T. S. occurs usually with a negative lepromine test. As a guide for " reactivity " of the patient to the infection and to the treatment, these two tests could, we feel, be usefully employed. Further comparative study of these two tests in leprosy is under contemplation by the authors of this paper.

S. T. S. IN TUBERCULOSIS

A small group of 17 cases of pulmonary tuberculosis was chosen for study. All of them had a positive sputum report for tubercle bacilli. As many as 8 of these, a little less than 50 per cent, gave an S. T. S. positive, or near positive. " Syphilis is the bed on which tubercle is born", as a wag once put it. This large percentage of S. T. S. in tuberculosis could again be either a simultaneous activity of the two granulomas, the tuberculous infection super-imposed on that of syphilis, or tuberculosis giving the positive reaction independently.

Another small group of 9 cases of clinically tuberculous meningitis was studied for the behaviour of their cerebrospinal fluids in the complement-fixation test (the W. R.). All gave a uniformly negative report, although the other physical, cytological and chemical tests gave the pathognomonic results for tuberculous meningitis.

THE SPINAL FLUID IN LEPROSY

Twenty-four leprosy patients whose blood gave positive S. T. S. were examined for the behaviour of their spinal fluids when put up for the Wasserman Reaction. Six out of the 24 gave a positive W.R. and one was "doubtful" positive. Of these, 4 gave a history of venereal disease. Five of the 7 were typed as neuromacular leprosy (the Cairo Conference terminology). All the other tests on these fluids were negative, *viz.*, the physical, cytological, and chemical. It appears justifiable to conclude from this, that though the nerve elements, peripheral certainly, and possibly the central in the spinal cord, come in for a large share of attention in leprosy, the condition for a positive complement fixation (or precipitin) test are not constant or *pari passu* with the nerve involvement.

SUMMARY

Two hundred and eighty-five subjects, clinically diagnosed as leprosy patients of one type or another, were investigated for their serum reactions in one (or both) of the common serological tests for syphilis, (S.T.S.) —the Wasserman and Kahn Tests. As many as 71 of these (about 25%) gave positive S. T. S. reactions. Many of these either did not respond to the well known anti-syphilitic treatments clinically, or serologically in their S. T. S. reactions. Anti-leprosy treatment with the sulphones, on the other hand, produced both clinical benefit and negative S. T. S., suggesting that the positive S. T. S. in the first instance were purely the result of their leprosy infection.

This paper discusses the possible reasons for the positive reactions, firstly in syphilis, and also in the granulomas, leprosy and tuberculosis, when they occur in the latter aberrantly. It is suggested that, in addition to the globulins in the antigens used in the tests and their corresponding antibody (globulins) in the serum, the lipoids both in the antigens and in the serum are as important in the causation of the positive reactions.

A small number (17) of active pulmonary tuberculosis cases, clinically unmixed with either syphilis or leprosy, and subjected to the S.T.S. gave as high as 50 per cent positives. The reasons for these positives could well be the same as in leprosy, *viz.*, the lipoid substances of the acid-fast envelope of the tubercle and leprosy bacilli and their anti-bodies in the serum of the infected individuals.

Twenty-four samples of the spinal fluid of leprosy patients, and nine of clinically tuberculous meningitis were put up for the Wasserman test.

In the first group (leprosy), 6 gave positive reactions and 1 'doubtful positive'. Three of these 7 gave no clinical history of venereal disease (syphilis), while 5 were classified as neuromacular leprosy (Cairo classification). Physical, cytological, chemical and other routine examinations of the 24 leprosy spinal fluids were negative. In the second, tuberculous meningitis group, the clinical diagnosis was confirmed by the pathognomonic findings in the routine laboratory examinations, but their W. Rs. were uniformly and unequivocally negative.

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ORIGINAL ARTICLE

THE ACTION OF FOLIC ACID ON THE ISOLATED INTESTINE OF THE GUINEA PIG

A PRELIMINARY COMMUNICATION

A. R. Govinda Rao *

The research on folic acid has been of intense interest to me, because of its great scientific and practical value. It offered the prospect of a specific form of therapy with a pure chemical compound of known molecular structure. Much work has been done and quite a number of publications have appeared recently from Spies[2,3,4,5], Berry and Garcia Lopez[2], *etc.*, about the hemopoietic activity of the *L. Casei* factor especially in nutritional macrocytic anemias and sprue. This paper is not meant to take up the vast subject of the anti-anemic properties of folic acid, but to confine itself exclusively to a possible suggestion regarding the mechanism of the beneficial action of folic acid on the gastro-intestinal system especially in sprue.

The observations of Spies[2,3] and his associates have made it abundantly clear that persons with sprue are profoundly benefited by the administration of synthetic folic acid. The acute manifestations of the disease subsided rapidly as the blood began its regeneration and the alimentary tract tended to regain its normal function. All the patients gave a history of having had diarrhea for periods of time ranging from four months to four years. The stools were light coloured, large, frothy, foul smelling, semiliquid or liquid and varied in number from 3 to 20. Bowel movements were accompanied by the expulsion of large amount of gas and by borborygmi. In many instances the bowel movements were preceded by colic indicating a spastic condition of the intestinal tract. Gastric analysis showed none of the cases to be histamine refractory but, on the contrary, the patients were found to have a normal or increased gastric acidity.

MATERIALS AND METHODS

Pieces of a guinea pig's ileum about an inch in length were dissected out and stored in cold Locke's solution. These, when ready for use, were suspended in a glass chamber containing Locke's solution, through which a continuous supply of oxygen was bubbled. The glass bath was maintained at 38 degrees throughout the experiment. The capacity of the bath was 200 cc., and all concentrations of drugs used in this experiment were based on this volume. The upper suspension of the

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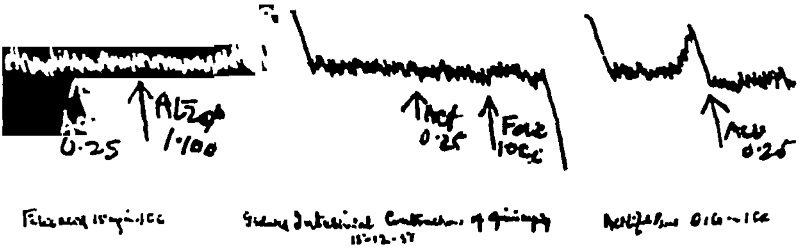

Fig. 1.—Reading from right to left the first arrow indicates where acetylcholine was put into the bath. Sudden upward stroke of the lever indicates a spasmodic contraction. Action after folic acid, 3 and 2 arrows shows no such contraction. Action after atropine, 5 and 4 arrows shows no such contraction. The gaps indicate when the bath was emptied and replaced by fresh Locke's fluid.

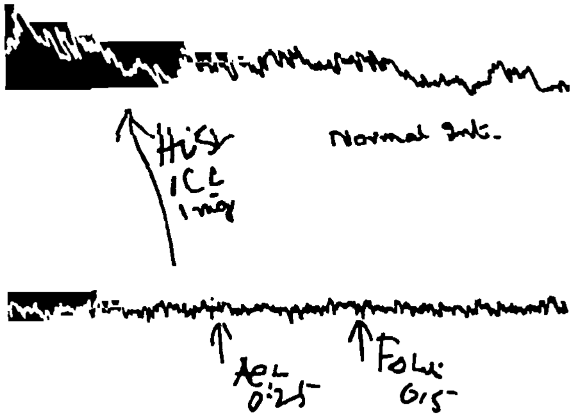

Fig. 2.—The upper record shows the spasm induced by histamine. The lower one shows that acetylcholine has no effect after folic acid.

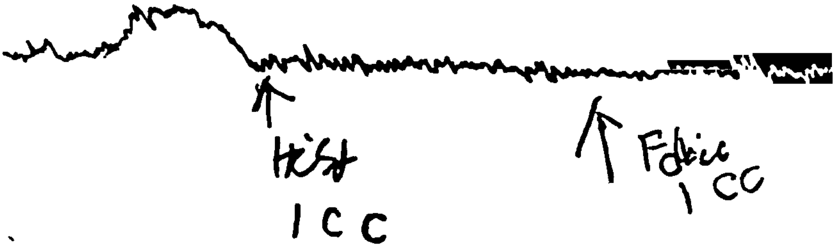

Fig. 3.—Shows that folic acid is unable to prevent the spasm induced by histamine in the isolated guinea [illegible]

intestinal strip was attached to a fine lever which was so balanced as to have as little weight as possible acting on the tissue. The preparation was allowed to work for at least 20 minutes in order to allow the tissue to adjust itself to the environment. The recording was done on a slow moving kymograph drum. The drugs were put into the bath fluid and the effects observed. Record No. 1 gives the effect of acetylcholine before and after folic acid and after atropine. Record No. 2 gives the effect of histamine and No. 3, histamine after folic acid.

From the records it becomes evident that folic acid (15 mg. per cc.) was able to completely prevent and neutralise the effect of acetylcholine (0.05 mg.) The intestinal spasm was completely prevented and normal contractions were established, while in the same concentration folic acid was ineffective in preventing the histamine induced spasm.

DISCUSSION

From the observations made till now, relationship between nutritional macrocytic anemia and sprue is very difficult to grasp. Differentiation actually may not be justifiable, and the final answers to the question, as to whether the conditions represent two distinct entities, or are identical, may have to wait until their etiology is more completely understood[5]. It has not been possible to adequately explain the exact mechanism of the action of folic acid either on the hemopoietic system or on the gastrointestinal system. It is not clear whether the primary action is on the former or on the latter system but it has been observed, in a number of cases, that *pari-pasu* with the improvement in the blood condition, the gastrointestinal symptoms also subside, the bulky frothy diarrhea gives place to well formed normal stools and the patient's nutritional condition becomes much improved[4].

The metabolic relationship between vitamin B_{12} and pteroylglutamic acid is still not understood. It seems evident from the experiments of Cartwright and associates[1], that in swine the peripheral blood, bone-marrow and chemical changes ascribed to pteroylglutamic acid deficiency are independent of vitamin B_{12} since these changes occur in the presence of the extrinsic factor in the diet and are neither prevented from developing nor alleviated by the administration of purified liver extracts or vitamin B_{12}. Under the conditions of the experiments reported in some of his previous papers, little or no hemopoietic response was observed following the administration of adenine, uracil, or thymine. Further, vitamin B_{12} in addition to thymine was ineffective in replacing the need for pteroylglutamic acid. There is now considerable evidence indicating an interrelationship between the metabolism of pteroylglutamic acid and ascorbic acid. Thus, it becomes more and more apparent that the exact mechanism and the site of action of folic acid is not very clearly understood.

CONCLUSIONS

It is possible that in sprue and similar nutritional macrocytic anemias there is a primary defect of the whole gastrointestinal tract as a result of which there is spasm and increased peristalsis, resulting in imperfect absorption of vitamins, food and the anti-anemic principle. The intrinsic factor has been demonstrated to be present in cases of sprue. Even when the extrinsic factor is supplied in adequate amounts to such cases, there is no therapeutic response because of the imperfect absorption of the anti-anemic principle. So, under such conditions, if folic acid is given, it has a definite beneficial effect on the gastrointestinal system, abolishes the spasm, relieves the augmented contractions and facilitates the absorption of the anti-anemic principle. When food is not rapidly hurried through the intestines but time is allowed for the pancreatic and intestinal enzymes to act, the fatty diarrhea is automatically controlled.

SUMMARY

On the isolated guinea pig's intestine, folic acid exerts a marked anti-acetylcholine effect almost like that of atropine and has a very little anti-histamine effect.

A possible primary beneficial effect of folic acid on the gastrointestinal tract in cases of sprue has been suggested.

Further work is being undertaken in this laboratory and the results will be published as soon as they are available.

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ORIGINAL ARTICLE

SPONTANEOUS CARDIAC LESIONS IN RABBITS

D. J. Reddy *

The etiology and pathogenesis of rheumatic fever are still subject to many hypotheses mainly due to the failure to isolate the causative organism. Menzer[7] in 1902 postulated an allergic mechanism to the streptococcal toxin as being responsible for the pathologic lesions of rheumatic fever. Vaubel in 1932, Klinge[7] in 1933 and Junghans in 1934, sensitised rabbits with small doses of horse serum by various routes and produced cardiac lesions in every way identical to the lesions seen in rheumatic fever. Inspite of the opposition staged by Aschoff[7] in 1935, the allergic theory of causation of rheumatic fever has not been discarded. Lesions similar to those of rheumatic fever were observed by Clark and Kaplan[7] in two fatal cases of pneumonia treated with antipneumococcal serum. Hopps and Wissler[4] produced polyarteritis nodosa of a generalised type in rabbits by repeated injections of horse serum. Polyarteritis nodosa has been reported by Freidberg and Gross as an occasional complication of rheumatic fever.

Polyarteritis nodosa, rheumatic fever, rheumatoid arthritis and disseminated lupus erythematosus are diseases where hypersensitivity plays a dominant role in the production of clinical manifestations and histopathological changes. The morphologic changes that occur in these diseases are characteristic of tissue reactions to hypersensitivity. Owing to basically similar morphological alterations, these diseases are bracketed under one group.

Hench and Kendall[4] of the Mayo Foundation, in 1949, demonstrated the beneficial results of cortisone and ACTH administered to patients suffering from rheumatoid arthritis. This has given further support to the allergic hypothesis as the causal mechanism in rheumatic fever and other allied diseases. In 1951, Germuth[2], Oyama and Ottinger showed that the diseases, result of the hypersensitive state induced in rabbits by injections of egg albumen, may be modified or completely abolished by the concurrent administration of cortisone or ACTH. Cortisone and ACTH seem to reduce the circulating antibody by inhibiting antibody formation and do not appear to promote antibody destruction.

The cardiac lesions in rheumatic fever or those produced in rabbits by repeated injections of horse serum are often divisible into acute and healing (chronic) phases. McKeown[7] in 1945 described the evolution of rheumatic lesions from human material and the intial lesion appears

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to be a focal necrosis of collagen followed by the migration of polymorphonuclear and eosinophil leucocytes. These are soon replaced by focal aggregations of large mononuclears some of which may be multinucleated. These lesions are distributed in the valves and septal tissues of the heart. McKeown[7] has also demonstrated the progress of cardiac lesions by killing rabbits at varying periods during sensitization with horse serum. She observed fibrinoid necrosis surrounded by eosinophils and round cells from the fourth to the twelfth day and after the fourteenth day fibrinoid necrosis was not conspicuous. In the healing phase, the Aschoff body was gradually replaced by a fibrous tissue scar.

The media of the coronary arteries also, are the site of fibrinoid necrosis and there is an infiltration of all the coats with eosinophils and round cells. Healing is marked by medial fibrosis of the vessel wall. McKeown[7] found arterial lesions in 88 per cent of her cases.

The clinician is fortunate enough in being familiar with the acute arthritic and cardiac manifestations of rheumatic fever while the pathologist, less fortunately placed, sees the healed scars of rheumatic cardiac lesions (stigmata of rheumatic fever) at autopsy, for rarely does the patient succumb to the acute manifestations of rheumatic fever. Spontaneous cardiac lesions in mice are reported by Lenke[3] and Loewe but they are said to be infrequent in rabbits.

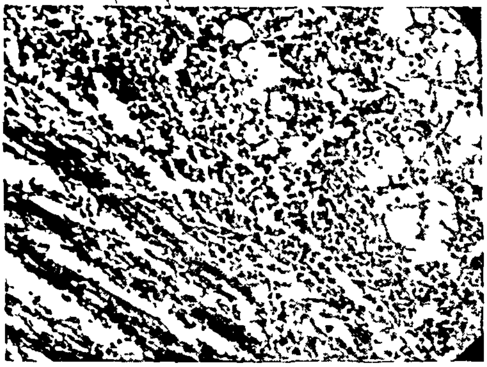
It is the dearth of pathological material of the heart in the acute phase of rheumatic fever in human beings and the rarity of spontaneous cardiac lesions in rabbits that has prompted me to record the observations made in a rabbit.

From April 1950 to August 1951, 21 guinea pigs and 4 rabbits were subjected to autopsy by me. Eleven guinea pigs were subjects of experimental fluorosis and 7 were subjects of ascorbic acid metabolic experiments. At the conclusion of the experimental study, they were killed by exposure to chloroform vapour. Three guinea pigs and 4 rabbits-subjects of atropine poisoning—succumbed to the toxic effects of atropine. The atropine was administered to all of them by the oral route. A complete autopsy was carried out in all these animals. Sections of the brain, lungs, heart, kidneys, adrenals, spleen, liver and bones in the ascorbic acid and fluorosis subjects, were examined histologically.

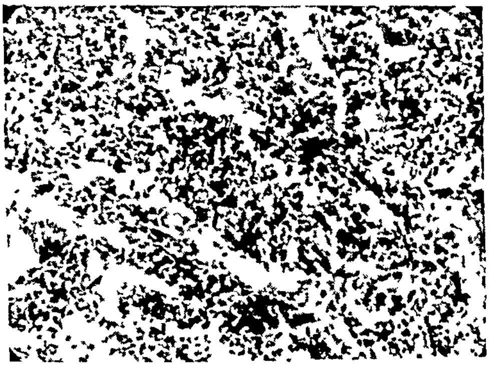
CASE REPORT

A male rabbit—R4, from the atropine poisoning series, at autopsy revealed whitish, friable, granular deposits over the visceral pericardium which was opaque and had lost its lustre. There was not much pericardial fluid. The mural and valvular endocardium showed no gross lesion. The heart was serially sectioned and the sectioned surface did not reveal any naked eye lesion in the myocardium.

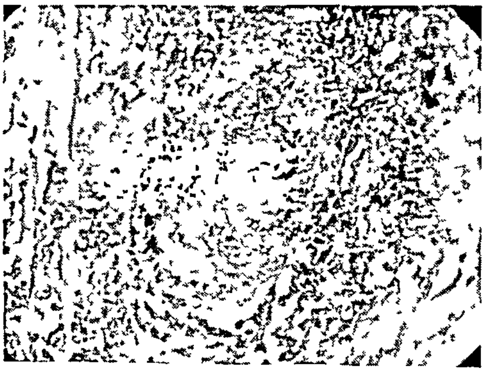
Hematoxylin and eosin stained sections from 5 blocks of the heart were studied under the microscope. The following observations were made.



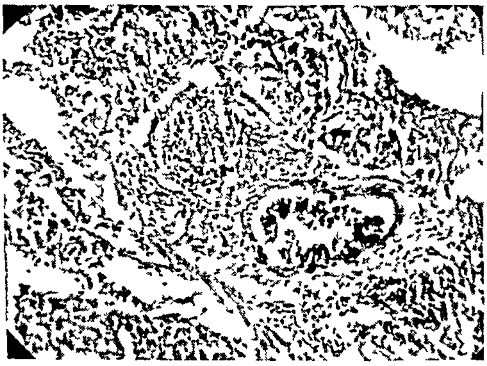
Photomicrograph 1.—Shows subepicardial tissue diffusely infiltrated with eosinophils and histiocytes. (H & E × 100).



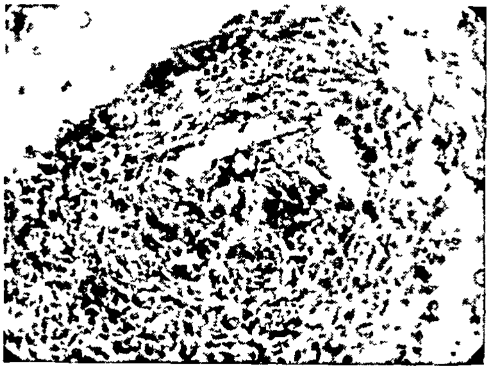
Photomicrograph 2.—Intact myocardial fibres could hardly be made out. They are fragmented. Eosinophilic and histiocytic cellular infiltration well seen. (H & E × 100).



Photomicrograph 3.—Aschoff body in its infant stage is seen in the myocardium. Oval area of fibrinoid necrosis bordered by histiocytes and eosinophils is well brought out. (H & E × 200).



Photomicrograph 4.—Shows a couple of coronary arteritis in the myocardium. Intraluminal thrombus in one and inflammatory reaction of the intima in the other vessel are well seen. (H & E × 100).



Photomicrograph 5.—Shows coronary artery. Arteritis infiltration with eosinophils and histiocytes of all the coats of the vessel wall and intraluminal thrombus are well seen. (H & E × 200).

Pericardium :—Fibrinous exudate with an abundant number of polymorphs and eosinophils was seen to cover the pericardium. The subepicardial fatty tissue was infiltrated with collections of eosinophils. In places these cells had blotted the existence of the original tissue. In between the lipoid cells of the subepicardial tissue abundant histiocytes were seen. (Photomicrograph 1).

Myocardium :—Both the auricular and ventricular musculature presented pathological changes. The myocardial fibrils were widely separated from one another. They did not stain bright pink and many of them were devoid of their nuclei. Sheets of myocardial fibrils were in minute fragments and were densely infiltrated with round cells and eosinophils. The cellular infiltration had completely masked the existence of even the fragmented myocardial fibrils. (Photomicrograph 2). In other places multiple foci of fibrinoid necrosis bordered by eosinophils and histiocytes were a conspicuous finding. (Photomicrograph 3). The histiocytes were characterised by deep staining, irregularly shaped nuclei, some of which were binucleate. The entire histological lesion compared well with the Aschoff body commonly seen in rheumatic lesions of heart. These varied in size and shape. some were small, while others were large enough to cover the entire field under the low power magnification. The majority were ovoid in shape. Heavy infiltration with eosinophils and histiocytes of the interstitial tissue and myocardial fibres were a feature. A few calcified spots in the damaged myocardium were seen.

Coronary Arteries : Coronary vessels of all sizes showed pathological changes. The entire circumference of the vessel wall was involved. Arteritis was noticed. Some vessels showed fibrinoid necrosis of the media. The lumen was filled with eosinophils and histiocytes. Many of these cells were seen tethered to the intima by fine fibrils. In some, the entire vessel wall was infiltrated with eosinophils and round cells and the lumen was partially occluded by a thrombus. (Photomicrograph 4 and 5). The endocardium was infiltrated with eosinophils. Sections stained by Gram and Acid fast stains showed no microorganisms in the cardiac lesions. Sections of the lungs, liver, spleen and kidneys revealed nothing remarkable.

DISCUSSION

The gross and histological findings of the rabbit heart were suggestive of pancarditis. The myocardium and coronary arteries were most affected. The histological findings in the myocardium bore a close resemblance to the Aschoff bodies commonly confronted in rheumatic fever. Although histiocytes were seen bordering each focus of fibrinoid necrosis, they were not large and multinucleated as are commonly met with in these lesions. This is accounted for by the very early nature of the lesions observed in several of the sections ; destruction of the myocardium appeared to be a dominant feature. This corresponds to the 4th to 12th day lesions often encountered in rabbits subject to horse serum injections.

The rabbit in question while being subject to atropine poisoning presented no clinical manifestations of ill-health though special care was not taken to rule out disease of the heart. Poisoning with atropine naturally precipitated its end.

The cardiac lesions described in the rabbit compare well with those seen in rheumatic fever. The cause of the observed lesions is difficult to state but one is tempted to speculate that they were the result of a hypersensitiveness to some factor in the rabbit's environment. Much of value for human pathology is to be learnt from a study of disease processes in animals. The extensive necrosis and diffuse infiltration of the myocardium with eosinophils and histiocytes and the arteritis and the thrombosis of the coronary vessels observed in the rabbit bear resemblance to the acute phase of rheumatic fever. Clinical manifestations of irregularities of the heart's action and the coronary insufficiency as possibilities of rheumatic affection of the heart in its acute phase in the human being is well emphasised by the observed findings in the rabbits.

SUMMARY

1. The literature on the etiology and pathogenesis of rheumatic and allied diseases is reviewed.

2. Spontaneous cardiac lesions in a rabbit are described and the probable clinical significance of rheumatic fever in its acute phase in the man is suggested.

ACKNOWLEDGMENT

I am grateful to Dr. A. R. Govinda Rao, M.B., B.S., M.S. Professor of Pharmacology, Andhra Medical College for affording me the opportunity to perform autopsies on his experimental guinea pigs and rabbits. I acknowledge with pleasure the help rendered by the Photo-Artist, Edwin.

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CASE REPORT

SUBACUTE COMBINED DEGENERATION IN AN INDIAN *

P. N. Chhuttani †

CASE REPORT

S. M. S., aged 58, from Amritsar, was admitted on the 13th October, 1950, with the complaints of (*a*) numbness and tingling in the upper extremities—duration 18 months, (*b*) numbness and formication in the lower limbs—duration one year, (*c*) weakness of the lower limbs—duration one year (*d*) frequency of micturition and precipitancy—duration two months.

The history of the present illness went back to about 18 months previous to admission when he fairly suddenly became aware of abnormal numbness in the upper extremities. Physiotherapy in the form of hot steam baths proved to be of no benefit and the numbness increased in intensity. During the next three or four months an insidious recovery followed, at the end of which the feeling of numbness and tingling was only very occasional ; this had continued till the time of admission.

For a year before admission he had been aware of a similar feeling of numbness and formication in the lower limbs also. In addition he had grown weak in the lower limbs, and for the previous 6-8 weeks had not been able to walk about.

For two months previous to admission the frequency of micturition and precipitancy had come on. He was constipated, moving every second or third day.

No relevant previous illnesses were elicitable. One month before the onset of complaints he had exposed himself to arsenical dust for about an hour, following which he got diarrhea, vomiting and fever. These subsided in 24 hours.

The family history was unilluminative. The diet had been good consisting of dal, roti, milk and eggs. He was a meat eater.

On examination at the time of admission, he showed a low grade anemia. Apart from the just palpable splenic enlargement, no other abnormality could be detected in the gastro-intestinal, circulatory, respiratory and other systems. On examination of the nervous system, the higher functions were normal except that he was a talkative person who was very concerned about details of his illness and possessed a mentality of a civil servant in abundance. His cranial nerves were normal. The upper extremities objectively showed no abnormality, apart from sluggish deep reflexes. Co-ordination and all forms of sensibility were undisturbed. In the lower limbs there was considerable loss of power specially in the dorsi-flexors of the feet. Clasp-knife rigidity was present in both lower limbs. The calves were tender on pressure. Co-ordination was defective in both lower extremities. Knee and ankle reflexes were exaggerated. Reflexes of the right side were brisker than those of the left. The plantar response on both sides was 'extensor'. The left lower abdominal reflex was absent, the rest were normal. His sense of pain, touch, and temperature was normal, while the vibration sense was lost upto the iliac crests. His sense of position was lost in the toes of the right foot and was very defective on the left side : it was normal in the ankle and knee joints. His gait was spastic, and he was unable to walk for more than a few yards.

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* Paper read at the Annual Conference of the Association of Physicians of India at Amritsar, in March 1951.

† From the Department of Medicine, Medical College, Amritsar.

The laboratory investigations showed the presence of a macrocytic anemia with a megaloblastic reaction in the bone marrow. The indirect Van den Bergh reaction was faintly positive. Gastric analysis showed the presence of histamine-fast achlorhydria ; stools showed ova of hookworms. The urine was normal. The cerebro-spinal fluid showed no abnormality. Serological reactions for syphilis in the blood and cerebro-spinal fluid were negative. The nails were examined for arsenic content but did not show its presence. Intensive therapy with crude liver extract and vitamin B_{12} was given and he was discharged on 4-12-1950.

During the stay in the hospital, he made considerable recovery. Paresthesias cleared up considerably and he was able to walk for some distance. Seen again two months later (on 14th February 1951), he stated that he had gradually worsened after discharge and although he was still on his feet he felt quite uncomfortable on account of paresthesias. He felt as if he was standing on thorns. Whenever anything touched his palms he felt as if needless had been stuck into them. He also felt a dragging sensation in the back muscles. He had not been receiving regular doses of liver and vitamin B_{12} as advised. On fresh examination, the changes seen from the previous findings were, no hyperalgesia in the lower limbs, less marked rigidity and improvement in the power of the various muscles. Deep reflexes in the lower limbs were still brisk. Plantar responses were equivocal. The left lower abdominal reflex was absent. The sense of position was still defective in the toes and vibration was lost upto the knees. Gait was still spastic though considerably improved than the previous examination.

Blood examination on 14-2-51 showed 1·12 million red cells per c.mm. with suspicious macrocytosis. He was advised to take 40 µg. of vitamin B_{12} regularly every four days till he was stabilized.

When artless doctor sees
No one hope, but of his fees,
And his skill runs on the lees,
Sweet spirit, comfort me!
When his portion and his pill,
Has, or none, or little skill,
Meet for nothing but to kill,
Sweet spirit, comfort me!
—Robert Herrick (From Medical World, 75 : 66, 1951).

BOOK REVIEW

Common Diseases, Their Causes and Treatment By Lieut. Col. M. S. Irani, F. R. C. S. (Edin.), I.M.S. (Rtd.). First Indian Edition. Cloth bound. Price Rs. 4-8. Pp. 210, with 3 illustrations. D. B. Taraporevala Sons and Co. Ltd., 210, Hornby Road, Fort, Bombay, 1952.

Lieut. Col. Irani has written a book on " Common Diseases, their Causes and Treatment". The object in writing it, is stated to be a reliable up-to-date medical guide for the layman. In 200 pages Col. Irani has covered many diseases and has started with obesity and weight reduction. Although technical terms have been avoided as far as possible, they are bound to, and have crept in, in large numbers. As a general revision, the practitioner and medical student will find it useful. The layman in India will not have the necessary background to understand it easily. However, the knowledge of diseases and methods of dealing with them, as developed by scientific and medical research in modern times, should prove to be interesting and fruitful to the inquisitive reader.

B. B. YODH.

CURRENT MEDICAL LITERATURE

MEDICINE

RUNNING EARS IN GENERAL PRACTICE, O'Brien, P. : The Pract. **168** : 268-271, 1952.

In this article the author deals with the problem of chronic otorrhea which is one of the most common complaints.

Basis of Treatment :—Chronic otorrhea may be frankly purulent, or it may be due to an eczematous condition. Before deciding the line of treatment, the following points should be considered :—(1) Careful history of the present condition and of previous ear, nose and throat complaints and to ascertain whether or not there is concurrent infection in these regions. (2) Thorough cleansing of the meatus before diagnosing or commencing of treatment. (3) A running ear, due to an eczematous condition of the meatal skin, needs initial treatment to combat the secondary infection. (4) Bacteriological examination has showed the following offenders as worthy of note :—*Prot. vulgaris*, *B. pyocyaneus* and *E. coli* and they can be recognised by their characteristic offensive odours. (5) Cases where there is concurrent infection in the throat, nose or sinuses, general treatment with antibiotics or sulphonamides will be indicated. (6) Topical use of antibiotics gives excellent results in suitable cases. (7) The advice of a consultant is necessary when the condition is complicated by polypi, large granulations, cholesteatoma, or obvious bone infection.

Cleansing of the Meatus :—It is usually cleansed by gentle syringing with lukewarm water, but if difficulty is encountered, where the matter present is hard and caked, hydrogen peroxide may be first instilled to break the mass, after which the ear is syringed.

Use of Antibiotics :—Penicillin ear drops.—The technique is as follows :—The meatus is first cleaned, then filled with 0.5 cc. of penicillin, 20,000 units per cc., and ribbon gauze is then lightly packed to prevent the fluid from running out and to serve the purpose of absorbing further discharge. This instillation is carried out, at first twice a day and then only once a day, when the Eustachian tube becomes patent, and consequently the physiological drainage of the middle ear is re-established. This is evidenced when the patient gets the taste of penicillin in the back of the mouth. If quick results are not obtained with penicillin, another antibiotic should be tried.

Chloramphenicol :—The meatus is cleaned first, and a 10 per cent solution of chloramphenicol in propylene glycol is then instilled into the ear and lightly packed with ribbon gauze. This is done daily or once in two days for a couple of weeks. The bitter taste of the drug becomes obvious to the patient, once it has penetrated through the eustachian tube, thus showing its patency.

Aureomycin gives similar results to chloramphenicol.

Eczematous Cases :—In this condition, the methods outlined above should be first tried, but if these medicaments aggravate the discharge, they should be stopped. Next, a wick moistened with aluminium acetate drops (N. F.) is used to reduce the edema and dry the meatal skin. Finally, the following lotion should be painted on the meatal skin with cotton-wool each day—oily lotion of calamine (N.F.) with added ichthyol 1 to 2 per cent.

ERIC COELHO.

TREATMENT OF TENIASIS WITH QUINACRINE HYDROCHLORIDE, Sodeman, W. A., and Jung, R. C.: J.A.M.A. **148** : 285-286, 1952. 3 refs.

The authors used quinacrine with success in the treatment of 11 patients with teniasis. On the day preceeding treatment, the patients received a milk diet to eliminate roughage and leave the worm exposed to the action of the drug. On that day at about 3 p.m. a purge was given to some patients. On the morning of treatment a cleansing saline enema was given, followed an hour later, by 0.6 to 1.2 Gm. of quinacrine hydrochloride, the dose being adjusted according to the age and size of the patient. Two to four hours after the administration of the drug, the purge was repeated and the dose modified according to the experience of the previous day. Food was withheld on the morning of treatment till a bowel movement was obtained. In all cases the drug was effective, 10 on initial trial, and the 11th patient when the drug was repeated. The only toxic symptoms were nausea and vomiting which were easily controlled. Quinacrine appears to be the drug of choice in the treatment of *Taenia saginata* infection.

Eustace J. de Souza.

TREATMENT OF TROPICAL ULCERS, Obrien, H. D.: B.M.J. **2** : 1544-1551, 1951, 34 references, 16 tables.

Discussing the treatment of tropical ulcers, Obrien first of all discusses the geographical factors concerned and the incidence of the condition in two districts of Tanganyika. He goes on to discuss the influence, that nutrition, circulation, trauma, infection and coincident disease has on the condition and describes the general treatment employed. This consisted of an adequate diet rich in protein, supplemented with 100 mg. of ascorbic acid daily and the fat soluble vitamins in the form of vitaminised shark oil or cod liver oil.

With regard to more specific treatment, various methods were used, including topical application of penicillin as a powder, consisting of sulphathiazole with mag. carb. pond., and as a cream. The powder and cream contained 10,000 and 500 units of penicillin per gram respectively. A lotion containing penicillin and bacitracin was also used. These preparations were applied once or twice a day, except in the case of the lotion in which the applications were increased to three or four a day.

Penicillin was also used parenterally. At first crystalline penicillin G., 25,000 units, in aqueous solution was given in three hourly doses. When, however, procaine penicillin became available this was employed instead, 150,000 units being given twice a day. The most satisfactory dosage scheme was to give penicillin from two to four days from admission, followed by four doses of 150,000 units at the time of grafting, two before and two after. Parenteral penicillin was found to eliminate pain and stench from nearly all cases within 24 hours. Where the ulcer had affected the bone, large doses of penicillin were used, and any bone operation was performed under a penicillin cover. The smallest quantity of penicillin used was about 0.5 mega unit, but this was in cases when " sulphatriad " was used concurrently. This latter sulpha combination proved much more expensive and did not show any special advantage.

Obrien concludes that the most satisfactory routine treatment for acute and subacute tropical ulcers is by occlusive plaster treatment combined with parenteral penicillin injections and skin grafting.

L. BANERJI.

TETANY AND EPILEPSY, Gotta, H.: Archives of Neurology and Psychiatry, **66** : 714-721, 1951 ; 4 figures and 27 references.

According to Sachs and Kalischer, tetany and epilepsy are two different entities and the two conditions may be found in the same patient ; according to some observers, the association of the two conditions is not a mere coincidence and tetany may be the causative factor of epilepsy. In 11 out of 25 patients suffering from tetany, observed by the author, symptoms of tetany appeared shortly after thyroidectomy and disappeared after a few days without any incidence of epileptic seizures. Fourteen patients had chronic tetany ; 3 of 14 patients were suffering from idiopathic tetany and 11, from post-operative tetany. All 3 patients of idiopathic tetany and 3 from the post-operative group suffered with epileptic seizures ; tetany had been present for 15 days to 5 years before symptoms of epilepsy appeared. Electroencephalogram tracings showed a few isolated spikes or slow waves in 3 cases ; the tracings were definitely abnormal in 3 other patients. In 1 patient the E. E. G. became normal with the treatment. The author is of the opinion that there is definite correlation between tetany and epilepsy, and hypocalcemia acts as a precipitating factor in epilepsy.

N. J. KOTHARI.

TOXICITY OF DIHYDROSTREPTOMYCIN SULPHATE FOR THE AUDITORY NERVE, Don, C., and Gregory, J. : Lancet **262** : 72-75, 1952. 15 references, 1 table.

The authors have reviewed literature on the toxicity of dihydrostreptomycin for the auditory nerve. The possible explanation was that the chemical purity was less, hence the hydrochloride salt was considered more toxic than the sulphate. An investigation was carried out in a series of twenty-six cases treated with dihydrostreptomycin sulphate, of established purity, intramuscularly, 1 Gm. daily. In two cases clinically insignificant labyrinthine damage was found. Four cases showed auditory impairment ; one with audiometric loss only, one with slight deafness, one with moderate deafness, and one with severe deafness. The results suggest that dihydrostreptomycin sulphate, although of a high degree of purity, is toxic to the auditory nerve. It is impossible to pass any judgment from the present series, whether auditory impairement due to dihydrostreptomycin is permanent or not ; but Glorig was of the opinion that all other types of perceptive or nerve deafness are permanent. As yet no case has been recorded of recovery of hearing after nerve damage from dihydrostreptomycin.

ERIC COELHO.

PROTECTION AGAINST X-RAY AND BETA RADIATION—LEAD GLASS FABRIC, Archer, V. W., Cooper G., and Kroll, J. G. : J. A. M. A. **148** : 106-108, 1952. 5 references, 6 figures.

The increased incidence of leukemia in physicians exposed to radiation is a matter of interest and concern. Ulrich's analysis of obituary notices for the ten year period 1935—1944 showed eight times as many deaths from leukemia among those listed as specialists in radiology. Henshaw reported that he had almost uniformly produced leukemia in mice by exposure to radiation. The authors felt that exposure of parts of the body not covered by conventional devices might be responsible for the high frequency of leukemia among radiologists. The quality or voltage equivalent of stray radiation was checked by Carl Braestrup of New York City and was found, contrary to general belief, to be practically the same as the primary radiation received by the patient.

The authors felt that some sort of gown should be constructed to cover portions of the body not presently protected. The material should be flexible enough to drape over the legs, shoulders and arms, resistant to cracking in sharply flexed areas, cleanable and fairly comfortable. The Owens-Corning Fiberglas research laboratory was visited where it was found that lead glass had been spun into thread for X-ray identification of sponges in surgical procedures. The laboratory was contracted to supply a quantity of cloth woven from thin lead glass thread. Experiments were conducted which showed that as far as protection from the x-ray beam was concerned, one thickness of lead glass fabric is equal in protection to 0.0035 mm. of sheet lead.

To determine the protection needed over various parts of the body large intraoral dental packets, uncovered in parts and covered in other areas, with one, two and three plies of lead glass fabric, were worn over eight different parts of the body. The location and amount of radiation received during 43 fluoroscopic examinations were noted. From these findings a gown was constructed which had the following thicknesses : abdomen, 5 layers, chest, 3, lower skirt, 2, shoulders to elbows, 2, lower arms, 3, back, open. The weight of the gown was 10½ lb. compared to the 11 lb. conventional apron. This gown though comfortable enough for work gave much more protection than the calculated requirement when one considers that the "tolerance dose" is 300 milliroentgens per week. The lead glass fabric is also very efficient in protecting against beta radiation of atomic fission products.

EUSTACE J. DE SOUZA.

GROWTH HORMONE AND CARBOHYDRATE METABOLISM, Editorial : The Lancet, **1** : 35-37, 1952, 26 references.

Experimental diabetes in animals, by the administration of growth-promoting extracts of the anterior pituitary, was first reported in 1932 ; further experiments were carried out by the administration of purified extracts. If cats and dogs are given diabetogenic extracts while they are still growing, the usual result is growth and not diabetes ; with long term treatment, diabetes begins to appear in puppies ; with large doses of insulin, such animals begin to grow again, which proves that the growth promoting hormone induces growth by stimulating the secretion of insulin. Young believes that metahypophyseal diabetes is purely pancreatic in origin and results from overwork exhaustion ; the idiohypophyseal stage results from the islet cells failing to keep pace with the greatly increased demand for insulin, initiated by the growth hormone. Anderson and Long attribute it to an inhibition of insulin secretion by the growth hormone ; another explanation is that the growth hormone stimulates the release of a hyperglycemic factor from the surviving alpha cells of the pancreas. The diabetogenic action of the hormone is different from that of ACTH. The nitrogen balance is usually positive in idiohypophyseal diabetes produced by the growth hormone ; it is negative in ACTH— induced diabetes. One case of hyperinsulinism was relieved by the administration of the growth hormone ; the opposite effect was noted in two other patients with organic hyperinsulinism. It is argued that certain forms of human diabetes and organic hyperinsulinism have a common basis in the oversecretion of the growth hormone. It is also recorded that ACTH relieved hyperinsulinism and improvement continued beyond the treatment period. The growth hormone or ACTH cannot as yet be ascertained as an important etiological factor in human diabetes.

N. J. KOTHARI

USE OF CORTICOTROPHIN AND CORTISONE IN ACUTE HOMOLOGUS SERUM HEPATITIS, Rifkin, H., Marks, L. J., Hammerman, D. J., Blumenthal, M. J., Weiss, A., and Weingarten, B. : Archives of Internal Medicine, **89** : 32-40, 1952, 3 figures and 13 references.

Four patients having acute serum hepatitis, showed no improvement when treated with the usual rigorous dietary, parenteral liver extract and a vitamin line of treatment. Nausea, icterus, and liver enlargement increased so much that it was thought necessary to try parenteral corticotrophin or cortisone therapy. Three patients received corticotrophin and 1 received cortisone in divided doses. The patient who received cortisone, improved within 24 hours, and 3 patients treated with corticotrophin improved in 36-72 hours. There was a sense of well-being and increased appetite and disappearance of gastrointestinal symptoms. The liver function tests disclosed a definite improvement and in some cases returned to normal within a short time. There is no evidence that the drugs exert any bactericidal or virucidal action. It is likely that increased psychic stimulation leading to sense of well-being, alertness and euphoria brought about the change with increased appetite and intake of diet of high caloric value. If there is any direct physiological change in the liver, it is not known. It is very likely that the drugs have a blocking or modifying effect on the action of the infectious agent on host cell ; suppression of anti-body may account for fall in temperature. Cortisone acts as a powerful stimulating agent for glycogen formation in the liver.

N. J. KOTHARI.

ALLERGY TO PITUITARY CORTICO-TROPHIC HORMONE, Feinberg, S. M., Feinberg, A. R., and Bigg, E. : J.A.M.A. **147** : 40-41, 1951: 5 references.

The authors report a case of a woman, aged 60, suffering from rheumatoid arthritis for 20 years developing serious allergic reactions to corticotrophin. The patient was treated with cortisone for 12 days but the clinical response was not adequate to cortisone therapy; it was decided to treat her with corticotrophin ; an injection of 25 mg. of corticotrophin brought about alarming reactions within 5 minutes ; there was generalised urticaria, angioneurotic edema, probably edema of the larynx, signs of asthma and profound shock; the patient recovered with epinephrine and other routine therapy. Corticotrophin (Armour) when injected 0.01 cc. intradermally in dilutions as high as 1 : 10 million brought about a whealing reaction ; corticotrophin of pork, beef and sheep origin produced the same reactions. Antuitrin, pituitrin, pitressin and pitocin when injected intradermally in high dilutions gave rise to a positive reaction of sensitivity to these substances. Corticotrophin peptide preparation supposed to be free from allergenic properties produced a high titer of skin reactivity. It is important to realize that the substance which is used to improve allergic reactions, is capable of giving rise to allergic reactions; it is because the action of corticotrophin is delayed and never adequate to prevent severe allergic reactions. As 12 days therapy with cortisone in the case described by the authors does not modify the allergic reaction to allergenic substance like corticotrophin, we should not depend on such agents to provide complete prophylactic measures against allergy. Some patients tolerate beef corticotrophin and do not show any reaction when it is administered clinically; this is due to species specificity. The hazard of allergic reaction must be kept in mind when dealing with corticotrophin. In this present case the patient was sensitised to corticotrophin by previous treatment of 12 injections of corticotrophin one year previous to the present time.

N. J. KOTHARI.

HORMONAL TREATMENT OF SIMMONDS'S DISEASE, Robertson, J. D., and Kirkpatrick H. F. W. : Lancet, **2**: 54-57, 1951 ; 2 tables, 3 figs., and 34 references.

Forsham *et al.* reported that ACTH had little response in cases of Simmonds's disease where the suprarenal cortex had undergone considerable functional atrophy. Bartter *et al.* believed that many effects of ACTH were due to the release of " sugar " hormone of the suprarenal cortex since an increase in the urinary corticoids was found with ACTH therapy. Knowlton *et al.* found slight retention of sodium and chlorides but constant alterations in the outputs of calcium, potassium and nitrogen or in tolerance to glucose after ACTH therapy. This therapy had no effects on the B. M. R.

Schrock *et al.* tried ACTH and cortisone in Simmonds's disease with rheumatoid arthritis ; both the drugs caused a sharp drop in the serum potassium level and both the drugs caused an elevation of blood pressure ; as therapy was combined with testosterone therapy the results were somewhat obscured. The authors report a case where both ACTH and cortisone were tried. The patient had a B.M.R. of 40 per cent, the pulse rate was 38; blood pressure was 100/65 mm. Hg.; excretion of 17-ketosteroids was 2.4 mg. in 24 hours; that of corticoids was 0.48 mg. in 24 hours ; 0.03 unit per Kg. of body-weight when injected intravenously caused a hypoglycemic coma within 25 minutes and the blood sugar level was 15 mg. per 100 cc. ACTH injection for 5 days caused a feeling of well-being and at times the patient was so euphoric that sedatives had to be given ; cortisone injection brought about severe bouts of depression ; one developed after three days of ACTH and during the administrations of cortisone ; blood-pressure rose from 95/65 to 125/75 mm. Hg. with ACTH but with cortisone no significant rise was observed ; ACTH and cortisone did not produce much alteration in the glucose tolerance test : ACTH caused a rise in the B.M.R. ; ACTH therapy caused an increase in urinary excretion of calcium, nitrogen, phosphorus, potassium and sodium. The same patient three years before ACTH and cortisone therapy. had been given implants of deoxycortone and of testosterone propionate and was taking thyroid 1-2 gr. daily ; he had not persisted with the treatment ; since Simmonds's disease is a deficiency disease, treatment with implants of deoxycortone and testosterone propionate and oral thyroid therapy keep the patient in good health ; since thyroid aggravates the signs and symptoms of suprarenal impairment a constant watch is necessary ; there is no advantage in ACTH and cortisone therapy over the implantation therapy.

N. J. KOTHARI.

MEASUREMENTS OF CERTAIN CARDIOVASCULAR RESPONSES TO ACTH AND CORTISONE IN MAN ; Hornitz, O., Sayen, A., Naide M., and Hollander J. L. : Am. J. Med. Sc., 1 : 669-671, 1951 ; 2 tables and 5 references.

18 patients of rheumatiod arthritis were studied before and during the treatment with ACTH and cortisone ; they were kept under control conditions from 6 to 15 days ; control studies were performed with 400-1150 mg. ACTH or 400-700 mg. cortisone. In 7, of 11 patients, an increase in the temperature of the fingers and not in toes was observed ; the increase was due to vasodilation ; there was a decrease in cardiac output ; a decrease in mouth temperature was noticed with ACTH ; subjective and objective improvement with decrease and lessening of pain was observed ; decrease in pulse rate and cardiac output was more striking with ACTH than with cortisone ; the increase in digital temp. was more marked with ACTH than with cortisone ; It is likely that a vasodilator effect may result from the relief of pain or from some direct vasodilator effect of the drugs ; Perera demonstrated a moderate rise of blood pressure caused by ACTH or cortisone in hypertensives or normotensives with rheumatoid arthritis and allied disorders.

N. J. KOTHARI.

TREATMENT OF THYROTOXICOSIS WITH METHIMAZOLE (1-methyl-2-mercaptoimidazole) Taylor, N., Teitelbaum M., and Large A. : Am. J. Med. Sc. **222** : 138-141, 1951 ; 2 tables and 6 references.

McGavak and associates found that methimazole is the antithyroid drug of choice in patients suffering from hyperthyroidism ; it is highly potent, rapidly active and non-toxic ; it inhibits the rate of intake of radioactive iodine. Revens and Rosenbaum treated 18 patients of hyperthyroidism with 2-5 mg. of methimazole at the interval of 8-12 hours ; the response was satisfactory. The drug is found 7 times as effective as propylthiouracil ; the return to the euthyroid state was rapid; there was no progressive enlargement of the thyroid gland; no increase in exophthalmos occurred in some cases. The authors selected 23 cases of hyperthyroidism for assessing the antithyroid value of methimazole; 17 patients had diffuse goitre with hyperthyroidism ; the average B.M.R. was 41 per cent; 12 became euthyroid on an average therapy lasting for 2 months ; the average dose of methimazole was 2 Gm.; at the end of the therapy the B. M. R. returned to normal. Six cases showed definite exophthalmic changes; only 5 cases showed slight enlargement of the gland. Six patients with toxic nodular goitre had a B.M.R. of 43 per cent when treated with methimazole; in 3 patients the B.M.R. returned to normal on an average duration of 87 days therapy and on an average dose of 3.025 Gm. Cardiac complications, present in 7 patients with diffuse goitre and 3 patients of nodular goitre, disappeared with methimazole therapy. Toxic reactions to the therapy did not develop in any patient during the six month observation period. Patients treated with iodine previously required a relatively short therapy of methimazole to bring about the euthyroid state. When the relapse occurs after the treatment with propylthiouracil, the authors recommend retreatment with larger doses of methimazole. With methimazole, the euthyroid state is reached in 40 per cent of the time and with about 6 per cent of the dose of propylthiouracil. Unlike propylthiouracil therapy, on which 2 patients were put and received 900 mg. of propylthiouracil, no patient was found resistant to methimazole therapy. All patients in the present series received 10 mg. of methimazole at 8 hourly interval.

N. J. KOTHARI.

PURPURA AND PANCYTOPENIA COMPLICATING ARSENOTHERAPY, Nelson, M. G. : B.M.J. 1 : 300-303, 1952, 12 references, 1 table.

Purpura and other blood disorders are rare complications of the treatment of syphilis by organic arsenicals. The author presents four cases of blood dyscrasia resulting from toxic effects of organic arsenicals as they were thought worthy of record. There was one case of thrombocytopenic purpura which recovered spontaneously. The other three cases showed a pancytopenia with marrow aplasia and they ended fatally. Dimercaprol in oil was administered intramuscularly in two of the four cases in the dosage of 1.2 Gm. spread over 6 days, but it had no apparent effect on the severe toxic manifestations.

ERIC COELHO.

GRANULOMATOUS ULCER OF THE NOSE TREATED WITH CHLORAMPHENICOL, Snddon, I. B. : B.M.J. 1 : 298-300 1952. 10 references, 3 figures.

The author describes a case of progressive granulomatous ulceration of the nose and face, in which a penicillin-resistant *Staph. pyogenes* was isolated from the lesion, at first in combination with hemolytic streptococcus and an avirulent corynebacterium ; later the staphylococcus was obtained in pure culture. Aureomycin was tried which prevented an extension of the infection, but a staphylococcus sensitive to the drug *in vitro* could still be recovered from the lesion. Chloramphenicol was then administered. This antibiotic produced a gradual recovery which was complete, and the staphylococcus disappeared from the ulcer. The author discusses the etiology of the condition and suggests that the granulomatous overgrowth is a non-specific reaction to staphylococcal infection and not to any one particular strain of the organism. It is concluded that chloramphenicol may be as good as, if not superior to, aureomycin in the treatment of staphylococcal infections.

ERIC COELHO.

CONTINUOUS METABOLISM OF HEMOGLOBIN IN THE RED CELLS OF PERIPHERAL BLOOD, Benard H., Gajdos A., and Gajdos-Torok M. : Nature, 167 : 989, 1951.

During the treatment of anemias, the increase of hemoglobin often lags behind the rise in the number of red cells.

The authors' experiments showed that a single dose of 15 mg. of folic acid or 20 µg. of vitamin B_{12} in rabbits induces a notable erythrocytosis in 6-24 hours. The hemoglobin value instead of increasing remains at its initial level with a consequent marked lowering of the colour index.

The increase in the number of red cells and the stationary hemoglobin value can be explained by the formation of new erythrocytes deprived of, or at least very deficient in, hemoglobin ; but examination of stained smears reveals a homogeneous tinctorial appearance in the red cells and systematic measurements of the red blood cells have shown no difference in the mean cell diameter during erythrocytosis.

From these observations, the authors believe that a redistribution of hemoglobin occurs between old and newly formed red cells, the nature of which is very complex and, no doubt, involves a degradation and resynthesis of the blood pigment operating in the hematopoietic organs. At all events, one must consider that the erythrocyte during the hundred odd days of its normal life, does not possess a fixed and immutable hemoglobin content ; this content can vary, particularly during certain hematopoietic incidents.

The protoporphyrin arising from the degradation of hemoglobin is not utilised as such for the resynthesis of the blood pigment. The rapidity observed in their experimental conditions of the turnover of hemoglobin during the erythrocytosis required an intense production of protoporphyrin to accommodate the speed of its resynthesis to the speed of its degradation.

In their experiments, folic acid or vitamin B_{12} injection was followed in a few hours by a considerable increase in the content in the red cells of free, non-hemoglobin protoporphyrin.

L. BANERJI.

THE PREVENTION OF ECLAMPSIA AND PRE-ECLAMPSIA, Hamlin, R.H.J. : Lancet, 262 : 64-66, 1952.

Seven steps are described which it is considered were responsible for the elimination of eclampsia and the reduction of the incidence of severe pre-eclampsia in a large women's hospital.

The successive steps were: (1) closer supervision of antenatal attendances ; (2) lectures on child birth and diet ; (3) increased antenatal supervision in the homes of country patients ; (4) co-ordination with local antenatal clinics ; (5) more frequent observation of patients' blood pressures ; (6) watching for digital edema ; (7) control of weight gain in mid-pregnancy by dieting.

It is normal for a young primipara with a low initial blood pressure to gain up to 8lbs. in weight between the 20th and 30th weeks of pregnancy. If she does not gain more she will almost certainly not have pre-eclampsia or eclampsia ; but if she gains more than 8 lbs., she will in all probability develop pre-eclampsia (mild or severe) or eclampsia.

Author's Summary.

ERIC COELHO.

SURGERY

CARCINOMA OF THE STOMACH, Swynnerton, B. F., and Truelove, S. C. : B.M.J. 1 : 282-292, 1952. 10 references, 13 tables and 2 figures.

The authors have reviewed the experience of the Radcliffe Infirmary from the case notes of all in-patients who were diagnosed as suffering from gastric carcinoma during the 12 year period 1938-49 inclusive. Adequate follow records were obtained for all of them. Twice as many men as women were affected and the peak incidence occurred in the sixties. There was great variation in the length of history before admission to the hospital. Nearly half were admitted within 6 months of their first symptoms, whilst one in five had symptoms lasting for more than two years. The commonest site of the neoplasm was the pre-pyloric region and the least common the fundus. Eighty per cent of the patients began their illness with symptoms referrable to the gastro-intestinal tract, the majority suffering from some form of indigestion. By the time the patients were admitted to hospital 50 per cent presented a lump in the epigastric region. The most accurate single diagnostic procedure was the barium meal. The finding of this diagnostic procedure was correctly interpreted in 90 per cent of cases. Achlorhydria was a common finding, independent of the age of the patient and site of malignancy. Normal or unusually acid secretions were also noted in some patients, and hence such findings should not be regarded as any bar to the diagnosis of gastric carcinoma. In most of the patients occult blood was detected in their stools.

Laparotomy was carried out in 63 per cent of the patients and resection of the growth in 30 per cent. During the second half of the period covered by this study, an increased proportion of cases were treated by resection. Nearly a quarter of the resected group were alive after five years, whilst only 1 per cent survived more than 5 years. Resection, therefore, was the only hope of prolonged life. Amongst the resected group, the prognosis depended upon the length of history. The prognosis was found to improve with increasing length of history. The age distribution of the patients, site of the lesion, etc., did not explain the finding, and the authors concluded that it was due to the occurrence of slow-growing carcinomata.

ERIC COELHO.

PEDIATRICS

PHENYLKETONURIA WITH A STUDY OF THE EFFECT UPON IT OF GLUTAMIC ACID, Woolf, L. I., Vulliamy, D. G.: Arch. Dis. Child., **26** : 487-494, 1951.

Phenylketonuria is an inborn error of metabolism characterized by the association of mental defects with the excretion in the urine of phenylpyruvic acid. It is inherited as a Mendelian recessive character occurring in children of cosanguinous marriages, the proportion of affected siblings being one in four. As fertility of phenylketonuric patients is low, it rarely occurs in both parents and offspring. Depression with persecutory ideas is more common amongst parents of these children than among the general population. The incidence of phenylketonuria has been variously estimated from 0.04 per cent to 1.2 per cent of mental defectives. It has not been demonstrated at birth, the earliest case being at 6 weeks. Some rather inconstant features should make one suspect phenylketonuria. There exists a facial similarity in many of the cases which is difficult to define. There is a relative lack of pigment in the hair and eyes, blonde hair and blue eyes being common. Cranial measurements tend to be small with no characteristic skull shape, the maxilla is large with wide spacing between upper and lower teeth. A dry papular eruption on the extensor surface or diffuse eczematous patches is common. Nervous complaints differ, with repetitive movements of the fingers being common. Petit mal, or less commonly, major epilepsy are frequent complaints. Cerebrospinal fluid examination, apart from a high content of phenylalanine, is normal, encephalograms show slight dilatation of the ventricles, the E. E. G. may show evidence of epilepsy. Liver dysfunction has been reported using the galactose tolerance tests. Demonstration of phenylpyruvic acid in the urine is simple to 5 cc. of urine 0.5 cc. of 5 per cent ferric chloride is added and a positive result indicated by the appearance of a deep green which reaches maximum intensity in three minutes and fades gradually. Though bodily health is unimpaired, mentally these patients have I. Q.'s below 20, and are idiots.

In view of encouraging reports on the use of glutamic acid in mental defects, the authors tried it in five cases of proved phenylketonuria. These cases were of two brothers from one family, two sisters from another family, and the fifth, a girl whose elder brother was a proven case of phenylketonuria (not treated by the authors). No significant increase in intelligence was found after continuous administration of 9 to 16 Gm. daily, of glutamic acid.

F. A. NAZARETH.

GANGRENE OF THE FOREARM IN THE NEWBORN, Brown, R. J. K., and Smith, S.R. N.: Arch. Dis. Child **26** : 574-577 : 1951.

The authors describe a very interesting case of gangrene of the forearm in the new born and review the literature. Gangrene of an extremity may be due to trauma at delivery as when a prolapsed hand is caught between the head and the bony pelvis causing a pressure necrosis, or may be due to infection. To date, 45 cases have been reported. Though amputation may have to be resorted to, treatment in many cases has to be conservative because of the uncertainty of the pathologic process. In the author's own case, a male infant was delivered by surgical induction at the 38th week of pregnancy of a 24 year old primigravida as she had toxemia of pregnancy. At birth, though the child cried well, the left forearm was motionless, cold and discoloured. Later, a deep constriction mark appeared just above the elbow, the left forearm was cold and no pulse was felt at the wrist and elbow. The lower extremities were cyanosed though the face, trunk and right arm were pink ; heart and lungs were normal. Conservative treatment was tried and having failed, amputation was done but the child succumbed two days later. Postmortem showed a dilated right heart with an antemortem thrombus in the auricle of the left atrium. The arch of the aorta at the point from which the left subclavian artery was given off was completely obstructed by a thrombus, the circulation to the descending aorta being maintained by a widely open patent ductus hence explaining the cyanosis of the feet. The authors suggest that the presence of the constricting band above the elbow was suggestive of pre-existent pressure *in utero*, while a dilated atrium in a failing heart might have been sufficient to encourage thrombus formation.

F. A. NAZARETH.

THE SIGNIFICANCE OF BRUSHFIELD'S SPOTS IN THE DIAGNOSIS OF MONGOLISM IN INFANCY, Wallis, H. R. E. : Arch. Dis. Child, **26** : 495-500, 1951.

The author discusses the historical evolution of signs in the diagnosis of mongolism. Among one of these signs, Brushfield, in 1924, described speckling of a white or very light yellow colour occurring as pinpoints near the outer margin of the iris generally placed at regular intervals in a ring. They were best seen in blue eyes, being absent in brown eyes. The author studied this phenomena in 7 mongol children. They all had blue eyes at birth with white spots on the iris which disappeared when the eyes changed to brown as the patient grew up. The author has also observed three normal children who presented the same phenomena. The diagnostic value of Brushfield's spots is therefore not great, except that their absence should disprove the diagnosis of mongolism.

F. A. NAZARETH.

VENEREOLOGY

RESULTS OF TOPICAL APPLICATION OF CORTISONE IN CONGENITAL SYPHILITIC INTERSTITIAL KERATITIS, Maddin, S.. and Danto, J. L. : Arch. of Derm. and Syph. **64** · 437-440, 1951, 8 references.

Though penicillin is effective in all types of syphilis including congenital syphilis, it frequently fails to bring about rapid and certain resolution of the inflammatory process in syphilitic interstitial keratitis, even when combined with fever therapy. In view of this failure of penicillin and the fact that the condition often interferes with schooling, the authors decided to evaluate the effect of the topical application of cortisone, as there were already favourable reports in literature of parenteral therapy with cortisone and corticotropin (ACTH).

The authors report two cases. Both were girls of 15 years and 13 years, respectively. The former had an unilateral, and the latter a bilateral affection. Both the patients received procaine penicillin (the first, 8.1 mega units, and the second 14 megaunits. Incidentally, serologic reactions with W.R. and Kahn Test and Mazzini were 4+in both cases. As penicillin failed to bring about substantial improvement, both subjective and objective, cortisone drops were instilled into the affected eyes. Cortisone acetate (2.5% ophthalmic suspension) was used by instilling one drope very hour during the working hours (7 a.m. to 9 p.m.) for 10 days. Necessary ophthalmic examinations were performed before and after the treatment. It was observed that the degree of improvement varied inversely with the duration of symptoms ; that treatment is effective, inexpensive and ambulatory. Besides, there is no danger of physiological alterations, as the amount used is too little. The exact mechanism of action of topically used cortisone is not known. However, events in the 2 cases treated, suggest that cortisone exerted its effect at a cellular-tissue level. Finally, the authors conclude with a note that cortisone does not supplant but only supplements therapy with penicillin in congenital syphilitic interstitial keratitis.

T. K. MEHTA.

DERMATOLOGY

HERPES ZOSTER TREATED WITH ACTH, Nickel, W. R. : Arch. of Derm. and Syph. **64** : 372, 1951.

The author, in this preliminary report, treated 5 cases of herpes zoster with ACTH. Three of them were above 50 years of age. Ten to 15 mg. of ACTH was injected at six-hour intervals. In all cases pain was relieved on receiving the third injection. The course of the skin lesions was unaffected by ACTH administration, but the relief of pain was maintained for 2 to 4 months, the period of follow-up. There is no mention regarding the average number of injections given.

T. K. MHETA.

FERDINAND VON HEBRA, Spitzer, E. : Arch. of Derm. and Syph. **64** : 282-283, 1951.

This is a short life sketch of Von Hebra the great dermatologist of the 19th century. He graduated from the University of Vienna in 1841 and soon became a houseman to Dr. Skoda, the then famous professor of internal medicine, at the Wiener Allgeweines Krankenhaus. At that time, patients with skin diseases were collected in a room called the " scabiesstation". Professor Skoda asked Hebra to look after these cases. This was the time when all skin diseases were considered as leprosy or venereal diseases and hence contagious. Patients were also treated cruelly.

So far there had been no effort to describe skin diseases in a systematic way. It was an era when medical science was governed by the theory of morbid fluids. Under such unfavourable circumstances Hebra studied skin diseases and expressed his basic conception as follows : " The objective symptoms are the letters which are written on to the skin by the disease : it remains our task to decipher the writings". Hebra succeeded in proving the parasitic nature of scabies by demonstrating the mite and by the experimental production of the disease by inoculation. Erythema exudativum and prurigo bear his name. He described eczema more thoroughly, and also " *scabies norwegica*". He was the pioneer who introduced local therapy for skin diseases at a time when his colleagues feared " pushing the disease into the inner organs " by such therapy.—He introduced unguentum diachylon hebrae and got international recognition for his water bed therapy. He was a great teacher, an observant clinician, an experienced therapeutist and above all, the founder of the famous Viennese School of Dermatology one hundred years ago, for which he earned world-wide recognition.

T. K. MEHTA.

SUCCESSFUL TREATMENT OF PEMPHIGUS WITH HEPARIN, Magner, J. P., Manson, R. C., and Pepple, A. : Arch. of Dermat. and Syph. 64 : 320-326, 1951.

After giving a comprehensive and concise description of the clinical picture and pathology of various types of pemphigus and tracing its history to the 17th century, the authors explain how they hit upon the idea of the heparin treatment of pemphigus. Epidermolysis bullosa, an hereditary affliction is characterized by the appearance of bullae at the site of trauma. In the words of the authors, " consideration of this factor in a condition wherein there is presumably a hereditary defect in the ' cement substance ' caused us to speculate on the probability of an acquired but identical defect in pemphigus." The ' cement substance ' probably consists, chemically, of hyaluronic acid and chondroitin sulfates. The latter are inactivated by the enzyme hyaluronidase, which normally is found in the testes. Investigators have noted that administration of hyaluronidase can simulate a rheumatic disease or can cause a relapse of a quiescent rheumatic disease. Bullae have been produced by the intradermal injection of hyaluronidase. On the theoretical basis that an acquired defect in pemphigus might be an analogue to the induced defect in experimental rheumatic diseases, the therapeutic use in pemphigus of a substance which inhibited the action of hyaluronidase was weighed. The following substances met this requirement : flavones, heparin, crude vitamin C, corticotrophin (ACTH), and cortisone. Heparin was chosen for the trial.

The authors' patient was a 30 years' old man suffering from pemphigus, probably the first attack. After all the routine treatment, including penicillin, aureomycin, chloromycetin, *etc.*, proved ineffective during a period of 5 months, the patient was put on heparin. First, heparin sodium (Abbot) was applied locally to ascertain the possibility of a hemorrhagic manifestation. There was no such sign after a trial of topical therapy for seven days. Then an intramuscular injection of the delayed absorption type of heparin (depo-Heparin, Upjohn Co.) was begun with a daily dose of 200 mg. for 20 days. The coagulation time during the period of therapy varied from 10 to 43 minutes. Within four days all lesions disappeared ; the patient became ambulatory and regained his appetite. No recurrence had occurred during the short follow-up of two months. The authors feel that the dramatic favourable response might be an induced one rather than a spontaneous remission.

In conclusion the authors emphasize the need for more trials before the drug can be accepted as really effective.

T. K. MEHTA.

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ESOPHAGEAL RESECTION FOR CANCER

CLINICAL CRITERIA OF OPERABILITY—REPORT OF EIGHTEEN RESECTIONS

E. J. Borges *

In July 1947 I reported my first three successful resections of the esophagus for cancer.[1] In this communication it is intended to record further personal experience with this operation.

It is now universally accepted that radiotherapy has proved disappointing as a routine treatment of cancer of the esophagus. Radical surgery, therefore, has to be considered in every case that is likely to be operable and to offer a reasonable operative risk. Unfortunately most patients come for treatment at a stage when only palliative measures are possible, and many of those that appear suitable for resection are found inoperable on exploration. This is the reason why the number of esophageal resections completed are few—in my own experience only 18 in five years. In the same period I have personally observed over 200 patients with cancer of the esophagus and subjected 26 patients to a fruitless exploratory thoracotomy. One patient in six therefore has been suitable for an exploratory operation, and of every three patients so explored in only one patient did the cancer prove to be operable. This poor operability rate could only be improved by earlier diagnosis of this disease.

CRITERIA OF OPERABILITY

Experience has taught that much operating time and bed space could be saved and many a patient spared an unnecessary exploratory operation if certain criteria are followed in selecting patients for operation.

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1. The general condition of the patient must be such as would enable him to stand a major surgical operation. Often a thin and emaciated man stands the operation better than an apparently sturdy but flabby individual. A low blood pressure is no contraindication. My third and last patients of this series (Case Nos. 14931 and L2522) had both a blood pressure of 100/60 mm. Hg. at the start of the operation and 80/50 mm. Hg. throughout most of the time of the operation. Several of the successful cases had systolic blood pressures around 100 mm. Hg. What is important is a good cardiac reserve which can be simply tested by the ordinary exercise tolerance test.

2. Advanced age is no contra-indication in itself. One of the successful resections in this series was performed on an old man of 73 years (Case No. K179).

3. The duration of symptoms should not be over 5 months. In all of the patients in whom the tumour was resected the duration of symptoms was less than three months, except in one patient whose, symptoms had started 5 months before operation. With a longer history of symptoms the chances of a tumour being found in an operable state are very small, and unless the other features of the case are exceptionally favourable for operation, exploratory surgery usually ends in disappointment, and waste of time and hospital bed space.

4. Pain that is present apart from the act of deglutition, and persists most of the time as a dull boring ache in the retro-sternal area or back, is in our experience a very definite indication that the growth has infiltrated outside the confines of the wall of the esophagus and the condition has passed into the inoperable stage.

5. The presence of fever that does not respond to antibiotics is another indication of a possible inoperable condition. It suggests the existence of mediastinitis or occult metastases in the liver.

6. Cancers situated in the mid-esophagus in relation to the root of the lung and arch of the aorta are so often found inoperable because of their adherance to important structures, that unless the other features of the case are very favourable I find it more economical as regards time and hospital bed-space not to subject them to an exploratory operation. Sweet[3] states that only 14 per cent of cancers situated in this region were operable in his experience.

7. Lesions situated at the lower end of the esophagus deserve exploration even if they appear clinically to be doubtfully operable. These patients never improve by radiotherapy. Even if an inoperable condition is found it is occasionally possible to relieve obstruction completely by a short-circuiting operation. The fundus of the stomach may be displaced into the thorax and an anastomosis (side-to-side) established between it and the esophagus above the obstruction. In this way the patient is saved the inconvenience of gastrostomy feeds.

OPERATIVE TECHNIQUE

In lower esophageal lesions it is usually advisable to explore the abdomen to establish operability from the abdominal aspect before proceeding to a major thoracotomy. A transverse epigastric incision is preferred as it can be extended outwards across the costal margin and into the intercostal space if a thoracotomy is decided upon. If an inoperable condition is found a gastrostomy is performed, and the abdominal incision closed. If there is no inoperable extension of disease in the abdomen the transverse incision is extended into an intercostal thoracotomy so that an abdomino-thoracic exposure is obtained.

In mid-esophageal lesions a left thoractomy is performed through the bed of the resected 6th rib. Operability in the thorax having been established the diaphragm is opened and the liver and paracardiac nodes are inspected. Conditions favouring resection being found, the operation is proceeded with ; otherwise the thoracic incision is closed and an abdominal gastrostomy performed if the patient is markedly obstructed.

Some surgeons advocate a right sided thoracotomy for approach to lesions in the mid-esophagus as they find it easier to deal with adhesions of the growth to the adjacent important structures from that aspect. This operation involves a preliminary laparotomy for mobilising the stomach and placing it in the thorax, after which the patient is turned on his left side and the thorax explored. If an inoperable condition is found, an esophago-gastrostomy is done above the obstruction, which obviates the necessity of a gastrostomy. I am not in favour of this procedure because I believe that esophageal cancer that requires active and difficult dissection from the esophageal bed is not worth the risk, trouble and time taken at the operation as almost all such patients die from recurrences or metastases within eight months of the operation. A carcinoma that does not require much dissection and has hardly extended outside the walls of the esophagus can easily be removed by the left-sided approach. If it is so stuck in its bed that it cannot be removed from the left side, I feel that resection is hardly justified.

The steps of the operation have already been described before.[2] Special care is taken to remove all the lymph nodes around the origin of the left gastric artery. The operation is completed by mobilising the stomach and transferring part of it into the thoracic cavity where an anastomosis is made between the stump of the esophagus and the fundus of the stomach. Resection of the mid-esophagus often necessitates anastomosis above the arch of the aorta, a procedure which carries a higher mortality than an operation in which an infra-aortic anastomosis is made.

CASE REPORTS

Altogether 18 esophageal resections were completed. There were two post-operative deaths, which will be discussed later. The first two patients had a Torek operation for cancer of the mid-esophagus : The whole thoracic esophagus was excised, the cervical esophagus was brought out in the neck and implanted in the skin as an esophagostomy to be used later for reconstructive esophagoplasty. However, experience with reconstructive operations of this nature with their repeated break-downs, and the prolonged hospitalisation involved soon convinced us that the Torek procedure was not satisfactory. Therefore the next 16 patients had a resection of the esophagus done with a displacement of the stomach into the thorax, and an anastomosis between the esophageal stump and the stomach. From the point of view of function, results have been excellent.

1. Case 14550. Mr. B. D. K., aged 45, with a carcinoma of the midesophagus. Resection of the esophagus (Torek operation) was done on 5 Nov. 1946. He recovered without complications and left hospital a month later. However, he returned after 3 months with a metastatic mass in the left iliac bone and went gradually downhill and died.

2. Case 14641. Mrs. M. B. M., aged 50 with a carcinoma of the midesophagus. Esophageal resection (Torek operation) was done on 29 Nov. 1946. She made a good recovery. In the next 12 months an ante-thoracic esophagus was being built for her in multiple stages. Before the completion of the final stage she one day had a severe hemoptysis and died 13 months after the resection. The cause was not ascertained as a post mortem examination was not permitted.

3. Case 14931. Mrs. A. D. G., aged 46 with a carcinoma of the lower third of the esophagus. A cardioesophageal resection and anastomosis was done on 7th Jan. 1947 and she made a good recovery. She went home on 12 Feb. 1947 well and able to swallow everything. She was kept longer in hospital than necessary as she was my first esophageal resection with anastomosis. She was last heard of in June 1947 at which time she was well and later she has been lost to the follow-up department.

4. Case J39. Mr. V. B. B., aged 46, with carcinoma of the midesophagus. On 4 March 1949 an exploratory thoractomy was performed. The growth was adherent to the aorta and hilum of the lung and an attempt was made to dissect it out because the general condition of the patient was fair. After much dissection the growth was freed and as part of it extended behind the root of the lung the esophagus had to be severed at the level of the aortic arch, and a supra-aortic anastomosis between the esophagus and stomach performed. At the end of the operation the patient passed into irrevocable shock and in spite of all measures expired 12 hours after operation. This was the first post-operative death in consecutive four cases.

5. Case K179. Mr. A. J. R., aged 73 with a carcinoma of the lower end of the esophagus. Resection and anastomosis was done on 14 Feb. 1950. There were many large metastatic nodes around the left gastric artery all of which were swept upwards and removed. The recovery was uneventful. The patient was able to swallow well all food and went home. He returned with abdominal metastases, and died 9 months after operation.

6. Case K1156. Mr. S. N. aged 55 with a carcinoma of the lower end of the esophagus. Resection and anastomosis was done on 16 May 1950. In the late post-operative period he developed an empyema which was drained. He recovered and went home. He is alive to-day almost 2 years (22 months) later, and able to swallow

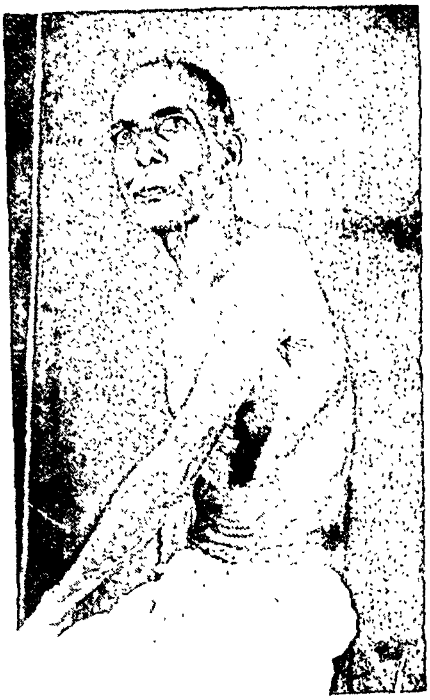

Fig. 1.—Case No. K1422. Photograph of patient 63 years old taken 2 weeks after resection of the esophagus and gastro-esophageal anastomosis. The oblique costal incision is visible.

Fig. 2.—Case No. K1422. Photograph of the same patient as in Fig. 1, taken one year after the operation.

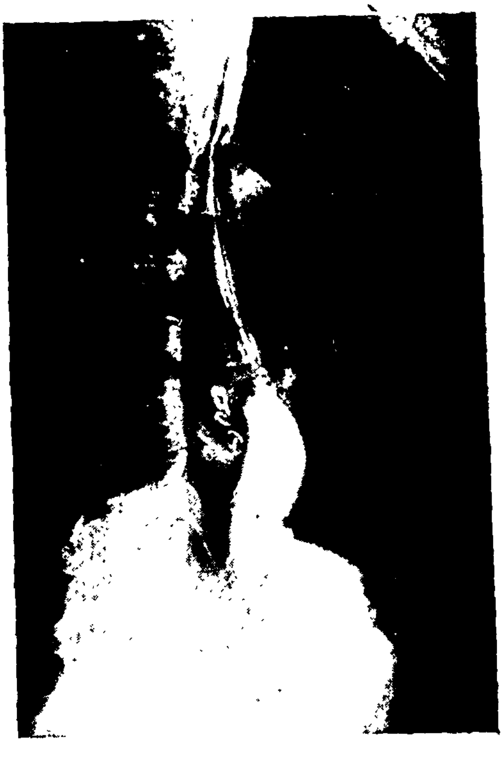

Fig. 3.—Case No. K1422. Roentgenogram after barium swallow given to the same patient as in Figs. 1 and 2. It shows the tubular stomach displaced in the thorax, and the site of anastomosis between the esophagus and stomach. The slight constriction at the lower part of the tubular stomach marks the opening through the diaphragm through which the stomach has been displaced upwards.

well. Recently he has experienced a feeling of obstruction which on investigation with barium proved to be a delay due to pylorospasm probably the result of vagus section. The anastomotic stoma functions well.

7. Case K1422. Mr. R. S. D., aged 63, with a carcinoma of the lower end of the esophagus. Resection and anastomosis was performed on 30 June 1950. He recovered and went home. He is alive and well and able to swallow all food to this date over 20 months after operation. (Figs. 1, 2, 3).

8. Case K1659. Mr. M. K. B., aged 50 with carcinoma of the lower third of the esophagus. Resection and anastomosis was easily done. Post-operatively the patient developed a tension pneumothorax on the side opposite the operation, apparently the result of a ruptured emphysematous bulla. The patient was a subject of asthma and had markedly emphysematous lungs. In spite of a continuous under water drainage which relieved him considerably the patient suddenly expired from cardiac failure 48 hours after operation. This was the second death in this series.

9. Case K2686. Mr. A. K. I., aged 45, with carcinoma of the lower end of esophagus. Resection and anastomosis was done on 13 Oct. 1950. There were metastatic nodes in the preaortic area and as much of the extension as possible was removed. He recovered and can swallow very well. He developed a flare up of an old tuberculous lesion of the left lung which is partly controlled by medical treatment. He had abdominal pain and was going downhill and presumably had extension of disease in the abdomen, 8 months after operation, when he was last heard of.

10. Case L462. Mrs. R. G. R., aged 53 with carcinoma of the lower third of the esophagus. Resection and anastomosis was done on 2 March 1951. She made a good recovery and was able to swallow well and went home. In May 1951 she developed jaundice and an enlarged hard liver and died in June 1951.

11. Case L807. Mr. K. L. D., aged 48 with a carcinoma of the lower end of the esophagus. Resection and anastomosis was done on 20 March 1951. There were a large number of metastatic nodes around the left gastric artery. The convalescence was uneventful and he was discharged from hospital on 2 April. He can swallow well, but now has a persistent backache and occasional abdominal pain. He may have metastatic disease in the retroperitoneal tissues.

12. Case L2090. Mrs. S. A. D., aged 50 with carcinoma of the lower third of the esophagus. Resection and anastomosis was done on 13th July 1951. She has made a good recovery and is able to swallow all food. She went home on the 15th post-operative day, and is well to date, 8 months later.

13. Case L2522. Mrs. P. aged 48 with a carcinoma of the lower third of the esophagus. Resection and anastomosis was done on 10 Aug. 1951. She made an uneventful recovery and went home able to eat solid food on 26 Aug. 1951. She is well to this date, 7 months later.

14. Case L3953. Mrs. S. V. T., aged 50 with carcinoma of the lower end of the esophagus. Resection and anastomosis was done on the 4th Dec. 1951. No complications occurred and she was discharged from the hospital on the 13th post-operative day. She is well and eating everything three months later.

15. Case L2783. Mrs. H. C., aged 52, with cancer of the lower end of the esophagus. On the 18th Dec. resection of the cardio-esophagus done, followed by anastomosis. She left the hospital on the 13th post-operative day and is well, able to swallow all food three months later.

16. Case L4295. Mr. M. M. H., aged 60 years, a feeble-looking Borah gentleman with cancer of the cardioesophageal region. Resection and anastomosis was done on 2nd Feb. 1952 and the patient discharged on the 12th post-operative day eating and swallowing well.

17. Case M17. Mr. C. S. S., aged 43, with cancer of the midesophagus. Resection and supra-aortic anastomosis was done on 4th Feb. 1952. He did well until the 6th day when he developed a leakage at the suture line without empyema. The leak drained out through the drainage tube. A jejunostomy was done for feeding. He was discharged 5 weeks after the operation with still a little leakage through the fistula. He was taking jejunostomy feeds as well as some liquid by mouth.

18. Case M638. Mrs. L. V. I., aged 56 years, with cancer of the mid-esophagus. Resection and supra-aortic anastomosis was done on 10th March 1952. There were no complications and the patient was discharged swallowing well on the 13th post-operative day.

COMMENT

This record of 18 cases of cancer of the esophagus treated by resection shows that the operation can be successfully undertaken without a high mortality. There were two deaths in this series of 18 cases (11 per cent). There has been no mortality in the last 10 consecutive cases of resection and anastomosis.

The first death took place as a result of shock from a very extensive dissection in an adherent growth which might have been best left alone. A supra-aortic anastomosis done in this case carried a higher risk of mortality. Sweet[4] of Boston who reported 213 cases in 1947 has a mortality of 24 per cent in patients in whom a supra-aortic anastomosis has to be done, and a mortality of 15 per cent in cases of anastomosis at a lower level (including both lower and mid-esophagus lesions).

The second death was the result of a tension pneumothorax from a ruptured bulla of the lung in an asthmatic patient with markedly emphysematous lungs. The added strain on the heart led to sudden cardiac failure on the third post-operative day.

The patients who survived did not cause much post-operative anxiety and had a comparatively easy convalescence. They are happy because they can swallow in the normal way and enjoy their food. None of the patients have developed a stricture at the anastomosis. I believe that this complication has been avoided by using interrupted cotton for both layers of sutures. As a result of this experience we are convinced that resection and intra-thoracic anastomosis between the esophagus and displaced stomach is the procedure of choice for esophageal cancer situated in the lower two-thirds of that organ.

As resection of the diseased esophagus can now be done without much risk it is imperative that patients should have the diagnosis of cancer of the esophagus made at the earliest possible moment. Permanency of cure after resection depends upon extirpation of the cancer before it has metastasised to the regional lymph nodes. It therefore behoves the general practitioner to have every patient with dysphagia investigated without undue delay, and resist the temptation to be optimistic and treat these patients for esophageal spasm.

SUMMARY

1. Economy of operating time and hospital bed space require that certain criteria should be followed in selecting patients with esophageal cancer for operation. These criteria are discussed.

2. The operative technique is briefly outlined.

3. Resections of the esophagus for cancer can be undertaken without a high mortality. This is illustrated by a record of 18 such resections with two deaths, the last 10 consecutive operations having been done without a mortality.

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STREPTOMYCIN IN TUBERCULOUS MENINGITIS*

A PRELIMINARY COMMUNICATION

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Since the discovery of the tubercle bacillus as the causative organism of tuberculosis by Robert Koch in 1882, a remedy for suppressing the organism has been searched for. Tuberculin, gold, copper and many other remedies came into vogue for short periods, to be ultimately discarded. Rich and Follis, in 1938, showed the inhibitory action of sulphonamide in experimental tuberculosis. Streptomycin was the first drug which showed any real activity against the *Mycobacterium tuberculosis.* Streptomycin was introduced in 1944 by Walksman, Schatz and Augie. In the same year, Feldmun and Hinshaw of the Mayo Clinic demonstrated the effectiveness of streptomycin in experimental tuberculosis. Since then the value of streptomycin in the treatment of various types of clinical tuberculosis has been demonstrated. Various reports suggesting the efficiency of streptomycin in tuberculous meningitis have been published.

This paper describes the results of the treatment of 43 cases of tuberculous meningitis under the care of one of us at the Sir Hurkisondas Hospital, between May 1949 and December 1951. The series includes all cases admitted in our unit and none has been excluded because of the severity of condition or shortness of the period in hospital. It includes even those cases who were moribund on admission and died in few days. Patients of all age groups were treated. The following table shows the number of patients in different age groups.

TABLE 1.—*Distribution of Cases in Age Groups.*

Age groups.	Under 1 yr.	1 to 1½ yrs.	2 to 2½ yrs.	3 to 4 11/12 yrs.	5 to 10 yrs.	10 to 15 yrs.	Above 15 yrs.	Total.
No. of cases. ..	10	10	3	2	5	2	11	43
Percentage ..	23.22	23.2	7	4.6	11.6	4.6	25.8	100

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It will be seen from the above table that 25 patients (58%) were under the age of 5 years while 18 patients (42%) were above the age of 5 years. The maximum incidence in the series is in the period of first 2 years (46.4%). Fig. 1 depicts the incidence curve.

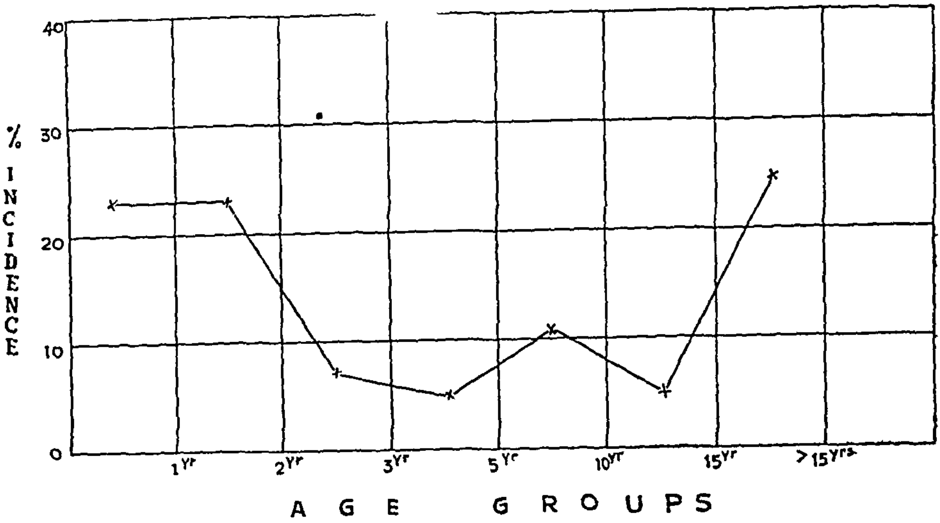

Fig. 1.—Age incidence

For the sake of convenience, the classification recommended by Medical Research Council of Great Britain[6] for grouping stage of the disease is adhered to in this paper :

Early : Non-specific symptoms, little or no clinical signs of meningitis, no paresis, consciousness present, general condition good.

Intermediate : Patients having signs of meningitis, slight paresis and unconsciousness.

Advanced : Deeply comatose or gross paresis.

Table 2 shows the number of patients studied in different stages.

TABLE 2.—*The Number of Cases at Different Stages.*

	Stage of Disease.		
	Early.	Intermediate.	Advanced.
No. of cases	4	30	9
Percentage	9	70.8	20.2

Table 3 shows the relationship of age to the stage of disease.

TABLE 3.—*Relation of Age to Stage of Disease.*

Stage of Disease.	No. of cases in different age groups.						
	Under 1 yrs.	Years 1—1.$^{11}/_{12}$.	Years 2—2.$^{11}/_{12}$.	Years 3—4.$^{11}/_{12}$.	Years 5—10	Years 10—15.	Years above 15.
Early							4
Intermediate ..	9	5	3	1	4	1	7
Advanced ..	1	5	—	2	1	—	—
Total	10	10	3	3	5	1	11

This shows that in all age groups patients of intermediate stage are more than the rest two stages.

The cases under review were diagnosed on clinical and cerebrospinal fluid findings. Increase in proteins and cells with lymphocytosis, the presence of a cobweb and diminution in sugar and chloride content, were considered as minimum diagnostic criteria. In most of the cases the cerebrospinal fluid was examined by the smear method for evidence of tubercle bacilli, but only in 3 cases were they demonstrated.

The different types of cases are included in the series. 32 cases were of meningitis alone while in the rest there was an associated tuberculous lesion. All the cases were, as far as practicable, investigated for evidence of tuberculosis elsewhere in the body.

TABLE 4.—*Type of Disease.*

Type of Disease.	No. of Cases.	Percentage.
Meningitis	32	75.2
Meningitis and Miliary Tuberculosis ..	2	4.6
Meningitis developing on a previous focus ..	9	20.2

Table 5 shows the associated tuberculous lesions in these cases.

TABLE 5.—*Associated Lesions.*

Miliary tuberculosis	2
Lung lesions other than miliary	3
Abdominal lesion	1
Cervical adenitis	4
Pleurisy with effusion	1

These figures are not necessarily accurate, for the absence of radiological evidence does not exclude miliary tuberculosis (Emery and Lorbar[4]). From the above tables (4 and 5) it seems that out of 43 cases, in 32 cases (75.2%) a primary tuberculous focus could not be detected, while 2 cases (4.6%) followed miliary tuberculosis ; 4 cases (9%) followed lung lesions, 1 case (2.3%) followed abdominal tuberculosis, while 4 cases (9.4%) showed lymphadenitis, and 1 case (2.3%) followed pleural effusion.

TREATMENT

The treatment given to these patients underwent various modifications with increasing experience. In addition to specific therapy, supportive treatment in the form of cod-liver oil, calcium, vitamins and symptomatic treatment, wherever necessary, was given.

Full diet was given to the patients unless there was any contra-indication. In some cases the problem of proper feeding and nourishment became difficult due to unconsciousness or persistent vomiting. In unconscious cases feeding had to be given by a nasal tube while in a few cases of severe persistent vomiting, feeds were given through a duodenal tube.

The specific therapy given to these cases was of two types. A group of patients (series A) was treated by streptomycin alone while the other group (series B) was given streptomycin and PAS. In the earlier part of the period under review, streptomycin was given intramuscularly only, but later it was given intramuscularly and intrathecally. The total daily dose of streptomycin varied according to the severity and the duration of the disease. In the early part, the daily dose was calculated at 30-50 mg./Kg. body weight, so that 2-3 Gm. of streptomycin were administered to an adult patient and 1/4 to 1 Gm. for infants and children. In subsequent cases, the dosage was calculated on the basis of 20-30 mg./Kg. body weight, so that 1-2 Gm. of streptomycin was administered to an adult. In the beginning, streptomycin was given in equal doses every 4 hours or 6 hours, but later on, the practice of giving two injections per day was followed. When improvement occurred, the daily dose was reduced to 10-15 mg./Kg. body weight. This was continued till the patient recovered completely. Streptomycin was then given once on alternate days for a further period of 3 months.

Intrathecal administration of streptomycin was given daily in the early series. In the recent series the frequency of intrathecal streptomycin was diminished. To begin with streptomycin was administered intrathecally for a period of 10 to 14 days and then once on alternate days. As the condition improved, the interval was further increased to once every fourth day or once a week. Finally the drug was abandoned when the cerebrospinal fluid returned to normal or almost normal. The total intrathecal dose was calculated at 1 to 3 mg. per Kg. body weight per day, never exceeding 100 mg. for an adult and 50 mg. for children. The method adopted by us nowadays is shown in Fig. 2.

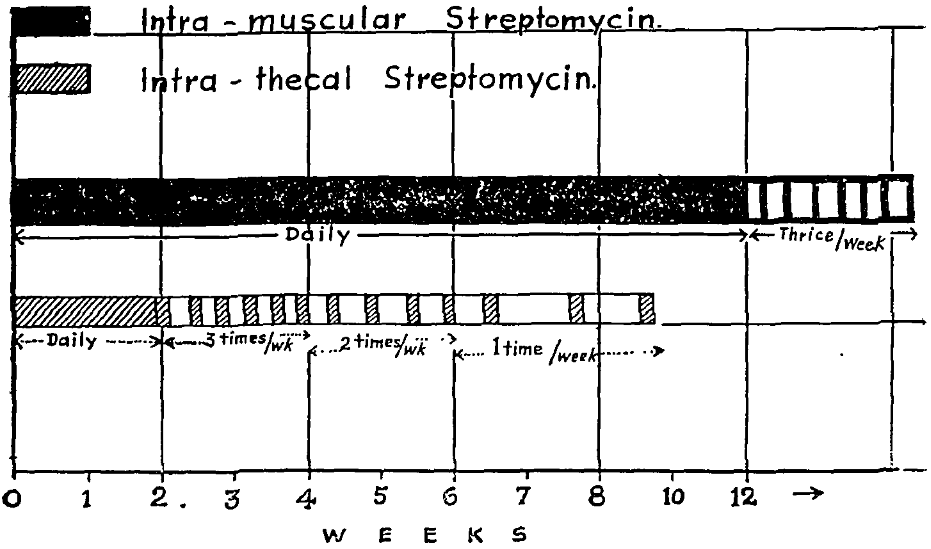

Fig. 2.—Method of treatment

In cases where PAS was added to streptomycin therapy, it was given in a daily dosage of 6 to 12 Gm. per day to adults and 1 to 4 Gm. to children. PAS was given in a small dosage for the first few days and gradually increased to the full dose in a week's time. If a patient showed intolerance to PAS an attempt was made to change the preparation. PAS had to be omitted in a number of cases showing marked vomiting.

Table 6 shows the number of cases treated in different ways.

TABLE 6.—*Modes of Therapy.*

Treatment given.	Series.	No. of cases.
Streptomycin alone	A	23
Streptomycin & PAS	B	20

In two cases promin was given as an adjuvant to PAS and streptomycin for a short period.

TOXICITY

It is difficult to find any toxic reaction to streptomycin in these cases. None of our cases showed any serious side effects to intramuscular therapy. We cannot say definitely whether the auditory and vestibular nerves were not affected as audiometric and vestibular function tests were not carried out. In the early part, streptomycin was given but now dihydrostreptomycin is administered. With intrathecal administration, a rise of temperature, irritability, headache, convulsions and increased vomiting were noted at times. Pleocytosis in the cerebrospinal fluid due to intrathecal administration of streptomycin is quite common but does not appear to harm the patients.

RESULTS

The overall figures for survivors and dead are as follows :

Seventeen (39.5%) died and 26 survived (60.5%).

Table 7 shows the period of observation of these cases during the stay in hospital.

TABLE 7.—*Period of Observation.*

Period under observation in hospital.	No. of cases.	Survivors.	Dead.
Under 1 week	17	1	16
1—2 weeks	2	2	—
2—4 weeks	6	5	1
1—2 months	5	5	—
2—3 months	6	6	—
3—6 months	7	7	—

It will be seen from the accompanying table that almost all deaths (except one) occurred in the first week after the institution of treatment. If cases treated with streptomycin for a period of less than one week are excluded, the survival rate will be very high. There were 26 cases treated for more than a week with streptomycin and 25 of them responded well.

In many cases we found it extremely difficult to persuade patients to stay in the hospital and continue treatment till there was complete cure. Once they felt improved, they insisted on being discharged and only continued intramuscular streptomycin at home.

Amongst the survivors, the period of observation varies from 13 to 185 days. Eight cases that survived were under observation for less than a month, while the rest (18 cases), for more than 30 days. The majority of the cases were under observation in the hospital for a period of 3 months, the maximum period being 6 months.

It is difficult to compare results with those of other workers for the literature on the subject is vast and individual variations, in the selection of cases, in deciding criteria of recovery and treatment, are very marked. However, the following table shows the results of certain other centres.

TABLE 8.—*Results* (*Comparison*).

Source.	No. of cases.	Period of observation.	Percentage of survivors.
Choremis, Zervos *et al*[3]	50	3 months.	48
Russell and MacArthur[11]	32	12 months.	44.5
MacCarthy and Mann[5]	43	16 months.	41
Medical Research Council (1950)[7]			
For early cases For advanced cases	369	10 months.	48 12
For early cases For advanced cases	369	2½ years.	48 10
Cathie and MacFarlane[2]: Series A (Streptomycin)	20	29 weeks.	25
Series B (Streptomycin) + adjuvants	40	29 weeks.	58
M. J. Shah and B. J. Vakil	43	3 months. (average).	60

The above table shows that our results compare favourably with those of other workers.

The follow up of these survived cases is under progress at present and the results at the end of a 6 months period will be communicated later.

On the basis of findings at the time of discharge, the survivors are graded as under :—

Grade I: Mentally and physically normal; cerebrospinal fluid normal or shows slight changes.

Grade II: Mentally and physically—slight changes, cerebrospinal fluid shows marked changes.

Grade III: No improvement.

By normal cerebrospinal fluid, we mean, one having not more than 4 cells and 40 mg. of protein and not less than 45 mg. of sugar.

This grading is arbitrary. Amongst the 26 that survived in the present series, 23 cases fall in first grade and 3 cases in third grade.

These cases seem to follow one of the four courses with the treatment. Some of them show gradual improvement with institution of treatment. In this series 23 cases showed this type of response. These cases showed signs of improvement in few days after the treatment was instituted. Signs of toxemia subsided and finally the cerebrospinal fluid became normal. None of these cases showed any mental defect or residual paralysis. Secondly, some cases gradually deteriorate inspite of treatment. There were 17 cases of this variety of response. Thirdly, some cases initially respond well to treatment, relapse again, and on further treatment they either survive or die. These two last types of courses are followed by a large number of patients of tuberculous meningitis treated successfully with streptomycin. One case (Case 20) included in the series is a relapse case. The patient was successfully treated in September 1948 with streptomycin. He was readmitted in January 1951 *i e.*, after 27 months. He was given streptomycin and PAS and responded well.

Case 23 is an example of a relapse case failing to respond. The patient was admitted in March 1951 and was treated for three months. She improved considerably and was discharged. She came back after 40 days. This time she failed to respond. She went home after a month where she expired in a week.

In series A, *i e.*, patients treated with streptomycin alone, there were 12 survivors (52%), while in series B, *i e.* cases treated with PAS and streptomycin, the survivors were 14 in number (70%). The following table shows the number of survivors in the different series.

TABLE 9.—*Survival in the Different Series.*

Series.	Survivors.		Fatal.		Grading of Survivors.		
	No. of cases.	Percentage.	No. of cases.	Percentage.	I	II	III
A	12	52	11	48	11	—	1
B	14	70	6	30	12	—	2
Streptomycin Intramuscular ..	6	44.5	8	55.5	5	—	1
Streptomycin Intramuscular & Intrathecal ..	20	60	9	31	18	—	2

The results with streptomycin given intramuscularly and intrathecally are better than when given intramuscularly alone as may be seen from the above table. When the drug was administered by combined route, the survival rate was 69 per cent while the survival rate was 44.5 per cent when it was given intramuscularly alone.

Tables 10 and 11 show duration of streptomycin therapy intramuscularly and intrathecally respectively and its relation to the response.

TABLE 10.—*Duration of Intramuscular Treatment.*

Days of Intramuscular Injection.	Grading of Survivors.			Dead.
	I	II	III	
Under 1 week	1	—	—	15
1—2 weeks	3	—	—	1
2—4 weeks	8	—	1	1
1—2 months	3	—	2	—
2—3 months	6	—	—	—
3 months	2	—	—	—

TABLE 11.—*Duration of Intrathecal Treatment.*

Days of Intrathecal injection.	Grading of Survivors.			Dead.
	I	II	III	
Under 1 week	6	—	1	10
1—2 weeks	3	—	1	—
2—4 weeks	3	—	—	—
1—2 months	5	—	—	—
2—3 months	2	—	—	—

Two facts emerge out from the above tables. Firstly, that these cases who could be given treatment for more than two weeks, mortality could be almost wholly prevented. Secondly, percentage of survival do not differ much with the route of treatment, when treatment is given for less than 1 week.

Importance of early diagnosis and early institution of therapy is shown in tables 12 and 13, and Fig. 3.

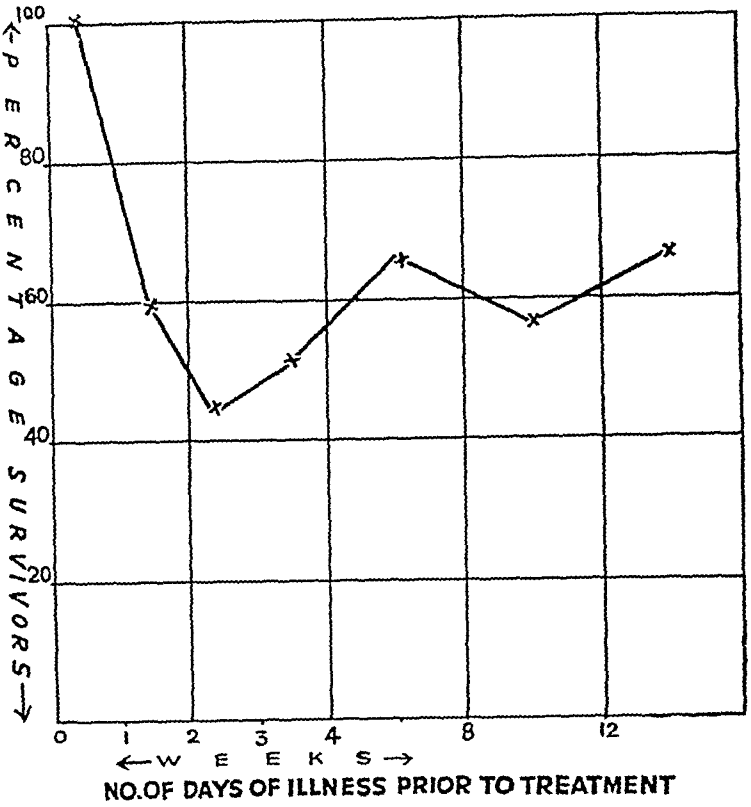

Fig. 3.—Survival Percentage

TABLE 12.—*Showing Results in Relation to Number of Days of Illness Prior to Admission.*

Days.	Survivors.	Percentage.	Fatal.	Percentage.
Within 1 week	5	100	—	—
1—2 weeks	3	60	2	40
2—3 weeks	4	45	5	55
3—4 weeks	3	50	3	50
1—2 months	6	66.6	3	33.4
2—3 months	4	57.2	3	42.8
More than 3 months	2	66.6	1	33.4

TABLE 13.—*Showing Results in Relation to Stage of the Disease.*

Grade of Survivors.	Stage of disease.			
	Early	Intermediate	Advanced	Total.
1	3	16	4	23
2	—	—	—	—
3	—	3	—	3
Total Survivors	3	19	4	26
Died	1	11	5	17
Total No. of cases	4	30	9	43

The results of treatment are better when therapy is instituted early in the disease—cases treated within one week of the onset of symptoms all survived. The percentage of survivors falls when the treatment is started later than 1 week.

Of the 4 cases admitted in the early stage of the disease, 3 showed grade I recovery (75%). Of the 9 advanced cases, only 4 survived (44%). Of the 30 cases of the intermediate stage in the series, 19 cases survived (62%).

From the limited number of cases in the present series it is difficult to say whether the type of the disease and other associated tuberculous lesions had any bearing on the outcome of treatment. The following table 14 shows the survivors in different types of tuberculous meningitis.

TABLE 14.—*Survival in Different Types.*

Grade of Survivors.	Type of the Disease.				
	Meningitis alone.	Miliary & Meningitis.	Lung Lesions.	Other Lesions (tubercular).	Total.
1	16	2	4	1	23
2	—	—	—	—	—
3	1	1	1	—	3
Total Survivors	17	3	5	1	26
Fatal	13	—	1	3	17

In two cases where promin was used as an adjuvant to streptomycin and PAS, the results did not seem to be in any way better than the others.

DISCUSSION AND CONCLUSIONS

Before the advent of streptomycin the prognosis of tuberculous meningitis was considered to be universally fatal. Streptomycin has been the first drug of real usefulness and hope. Since then, though many cases of tuberculous meningitis have died inspite of treatment and though some have succumbed after showing initial improvement, there are cases which have been cured and remained well. Yet the antibacterial therapy of tuberculosis has lagged behind that of many other bacterial diseases inspite of streptomycin, PAS, sulphones and other compounds. Streptomycin is highly bacteriostatic and partly bacteriocidal against the tubercle bacilli. The chief drawback is the high incidence of bacterial resistance to the drug after its use for a few weeks.

The reports of the Medical Research Council[6,7] and the Ministry of Health of Great Britain[8] recommend the administration of streptomycin by double routes, namely, intramuscular and intrathecal. They found the best results when intrathecal injections were given for more than half the days of intramuscular therapy. When intrathecal administration was increased to more than 75 per cent of days of intramuscular therapy, the results were no better. The mortality rate in their series for early cases was 50.7 per cent while for all cases was 71.4 per cent. On follow up, survivals from early cases show a better prognosis than those from advanced cases.

We have included all cases in this series irrespective of age and stage of the disease. We feel that the exclusion of cases from a study lead to wrong statistics.

In our series the overall survival rate was 60 per cent. Again, the survival rate in younger age groups (under 2 years) is better than that in older age groups. The incidence of tuberculous meningitis is higher in younger age groups (under 5 years) the maximum being in first 2 years.

We find that when treatment is instituted early, *viz.*, within 8 days of disease, the chances of survival are very high. For the rapid establishment of diagnosis, first class laboratory help is essential. In many cases a clinical suspicion is important in detecting early cases. Some of the early symptoms observed in this series were pyrexia, vomiting, apathy, malaise, drowsiness and headache.

Convulsions and paralysis occur a little later. In early stages we have often found no neurological signs. There may be a doubtful Kernig's sign or Brundzinski's sign, brisk reflexes and diminished superficial reflexes. Cranial nerve paralysis occurs in advanced cases.

Results were better of patients in the early stages. We have not been able to search for acid fast bacilli by cultural or guinea pig inoculation methods in these cases.

The best results are found in those cases treated by combined streptomycin and PAS therapy. Streptomycin must be administered intramuscularly and intrathecally. We find that the method of giving intrathecal injection daily to start with and increasing the interval as the condition improves, gives good results. We had satisfactory results with the usual recommended dosage.

We do not find any influence of associated tuberculous lesions on the prognosis of these cases.

Promin was found not to be much effective.

CASE REPORTS

Table 15 gives the main features of these cases. The following five cases are illustrated in detail.

I. Case 17.

A female patient aged 44 was admitted in an unconscious condition on the 13th July, 1950. The patient had continuous fever for the last 18 days and became unconscious a day before admission. On examination, the patient was found to be semi-conscious; motor power was diminished. Deep reflexes could not be elicited. There was neck rigidity and Kernig's sign was absent. The plantar response was flexor. On investigation, blood and urine findings were normal; cerebrospinal fluid showed 250 mg. proteins, 17.5 mg. glucose, 579.9 mg. of chlorides, 308 cells with predominant lymphocytosis. Nonne-Apelt reaction was positive.

The patient was given nasal feeds. Streptomycin was given 1 gram intramuscularly daily and 30 mg. intrathecally, daily for 7 days. The total amount of streptomycin given was 210 mg. intrathecally and 7 grams intramuscularly in 7 days.

The patient's condition deteriorated gradually, and she expired on the 7th day of admission.

II. Case 25.

A female child (D. R.), aged 3 years, was admitted to the hospital for continuous fever of 3 weeks duration. She had vomiting for one week, cough with expectoration for 2 days and was semi-conscious for one day.

On examination, the patient was semi-conscious, pupils reacted sluggishly to light. Neck rigidity was present. Kernig's sign was absent. Both the plantar responses were extensor and deep jerks were absent. On investigation, blood showed leucocytosis (9,600 cells/c.mm.) with 55 per cent lymphocytes. Cerebrospinal fluid showed increase in proteins (75 mg.) and decrease in glucose 32 mg. and diminution in chlorides (618.4 mg.), 179 cells with predominant lymphocytes. A roentgenogram of the chest showed haziness at the left upper lobe. The sedimentation rate was 21 mm./net.

The patient was given full diet, vitamins and calcium, ½ gram streptomycin was given daily intramuscularly. Intrathecally, streptomycin was given in 12-30 mg., dose daily for the first two weeks, later, on alternate days, and finally once a week. The total amount of streptomycin given was 40 Gm. intramuscularly and 880 mg. intrathecally. The patient was under observation in hospital for 3 months and was discharged with no clinical signs and normal cerebrospinal fluid.

III. Case 23.

A female, (D.H.) aged 42, was admitted on 26/3/51 with a history of continuous fever of 1½ months, cough, headache and vomiting. On examination, the patient was found to be semi-conscious. Lymph nodes all over the body were enlarged. There was slight neck rigidity. On investigation, the cerebrospinal fluid showed an increase in proteins (75 mg.), decrease in chlorides (631 mg.), and normal glucose (50 mg.); 127 cells with lymphocytosis. A roentgenogram of the chest showed miliary tuberculosis of both lungs. The patient was given a full diet and supportive therapy in the form of liver extract, vitamins and cod-liver oil; 75 mg. streptomycin was given intrathecally daily. Intramuscular streptomycin was given in 2 gram/day doses for 1 month, then it was reduced to 1 gram per day. PAS was given, 6 grams daily. Intrathecal administration was decreased to once every 3rd day and later once a week, as the condition improved. The total streptomycin given was 159 grams (2.6 gram. intrathecally). The patient was clinically better. The cerebrospinal fluid improved a great deal. She was in hospital for 7 months and then discharged. She was re-admitted a month later with a relapse. Streptomycin, intramuscular and intrathecal, was given but it failed to respond. She was under observation for one month. She expired 8 days after discharge from hospital.

IV. Case 43.

A female (K. J.) aged 21 years was admitted on the 4th of December 1950 for irregular fever of 6 weeks duration, cough, and pain in the right iliac fossa. On examination, she was found to have a right sided pleural effusion. She was treated for the same; 3 weeks after admission she started complaining of a headache. Her cerebrospinal fluid showed an increase in proteins (125 mg.), diminution in glucose and chlorides (40 mg. and 620 mg. respectively), 106 cells with lymphocytosis.

The patient was given a full diet, vitamins *etc.* 50 mg. streptomycin was given daily, for 7 days. Later on it was given thrice a week for 2 weeks. Then twice a week or once a week. Intramuscular streptomycin was given (128 grams); intrathecal —750 mg. She showed marked improvement. Her headache disappeared, cerebrospinal fluid became normal. She was followed up at the end of 12 months and clinically, found to be normal. Cerebrospinal fluid showed no changes.

V. Case 36.

A female child of 1 year was admitted on 6th February 1951 for fever of 6 days duration. A roentgenogram showed an opacity at the left base. On examination, there was neck rigidity, cerebrospinal fluid showed 125 mg. proteins, 28 mg. glucose, 608 mg. chlorides and 100 cells, lymphocytes predominant. She was given a milk diet; ¼ gram PAS daily, streptomycin ¼ gram intramuscularly daily for 36 days. 10 mg. streptomycin was given intrathecally on alternate days. The total streptomycin given was 9 grams intramuscularly and 20 mg. intrathecally. She showed no improvement and went home on 6th March 1951.

SUMMARY

The results of 43 consecutive cases of tuberculous meningitis are presented. The immediate survival rate was 60 per cent, (*i e.* 26 cases survived). Of these 26 cases, 23 were classed in Grade I and 3 cases in Grade III. None of them had any residual mental defect on discharge from the hospital. Follow-up results of five cases are given. The survival rate of those under 2 years is better than those above 2 years. Institution of early therapy is essential to get the best results. The importance of early diagnosis and early non-specific symptoms are stressed. At present the ideal method of treatment seems to be combined therapy

TABLE 15.—*Case Reports*

Case No.	Age	Duration of illness prior to adm.	Evidence of TB else where	Stage	Symptoms.	Signs.	Investigations		Treatment.					Adjuv-ants.	Ped. of obs. in days in		Results.
									Streptomycin			P A S					
							Chemis-try	Smear	IM.	IT.	Total	Daily.	Total.		Hosp.	after dis.	
1	1¼ yr.	8 days	..	Int.	F., C., Unconsciousness.	N. R. Kgs+pupils not reacting to light.	+	..	¼ Gm. q.d.s.	10 mg. alt. dys.	10 mg. I. T. 2 Gm. I. M.	..	..	..	7	..	Expired.
2	52 yr.	10 days	..	Int.	H., V., C., F.	VII Left paralysed Kgs+N.R.	+	A.F.B.+	¼ Gm. q.d.s.	75 mg. dly.	2 Gm. I.M. 225 mg. IT	..	..	..	3	..	Expired.
3	35 yr.	15 days	..	Early	H., V.	..	+	..	½ Gm. b.d. later t.d.s.	75 mg. dly.	20.5 Gm. I.M. 375 mg. I.T.	..	..	..	15	..	Improved. C.S.F. showed slight changes Grade I.
4	4 yr.	21 days	..	Int.	C., F.		+	..	¼ Gm. b.d.	..	5 Gm. I.M.	..	..	..	13	..	Clinically improved C.S.F. slight changes Grade I.
5	10 mth.	2 days	..	Int.	V., C., F., Unconsciousness	N. R.	+		¼ Gm. b.d. later 1/3 Gm. b.d.	..	13 Gm.	..	..	..	19	20 mth.	Clinically improved C.S.F. slight changes Pt. fine after 20 mths. C.S.F. Normal Grade I.
6	9 mth.	1 mth.	..	Int.	C., F., Unconsciousness	N.R. Kgs+	+	A.F.B.+	¼ Gm. b.d.	..	2 Gm.	..	..	..	3	..	Expired.
7	48 yr.	3 mth.	..	Int.	H., V., F.	N. R.	+	A.F.B.+	½ Gm. b.d.	75 mg.	23½ Gm. I.M. 450 mg. I.T.	..	..	..	59	..	Expired.
8	30 yr.	2 mth.	..	Early	H., F.	..	+	..	½ Gm. b.d.	50 mg. 3 inj.	42 Gm. I.M. 150 mg. I. T.	2 Gm. t.d.s.	258 Gm.	..	68	..	Clinically improved C.S.F. slight changes Grade I.
9	22 yr.	10 days	..	Int.	H., V., F.	N. R. Kgs +	+	..	½ Gm. b.d.		4½ Gm. I.M.	2 Gm. t.d.s.	30 Gm.	..	5	..	Expired.
10	4 yr.	2 mth.	..	Adv.	H., V., F., Unconscious	P.E.	+	..	¼ Gm. b.d.		45 Gm.	2 Gm. t.d.s.	..	..	70	..	Clinically Improved C.S.F. slight changes Grade I.

11	6 yr.	3 days.	..	Int.	V., C., Unconsciousness	N.R. P. E.	+	..	¼ Gm. b.d.	..	16 Gm.	..	..	..	26	3 mth.	Clinically Improved C.S.F. slight changes. Expired after 3 mth. Grade I.
12	1¾ yr.	45 days	..	Adv.	C., S., Semiconscious Fever	——	+	..	¼ Gm.		20 Gm.	½ Gm. t.d.s.	6 Gm.	..	38	..	Clinically Improved Grade I
13	20 yr.	18 days	..	Int.		N.R.	+	..	½ Gm. t.d.s.	..	4½ Gm.	..	..	..	15	..	Expired.
14	1½yr.	1½ mth.	..	Adv.	F., Squint R. eye. Unconscious	3rd Rt. side Paralys P.E.	+	..	¼ Gm. b.d.	15 mg.	6 Gm. 180 mg.	..	..	..	13	..	Clinically Improved. Grade I.
15	8 mth.	1 mth.	..	Int.	C., F.,	N. R.;Kgs.+	+	..	1/3 Gm dly.	..	12 Gm. I.M.	..	..	..	37	..	Not Improved. Grade III.
16	9 mth.	2 mth.	..	Int.	V., C., F., Unconscious	N.R. ; Kgs +	+	..	¼ Gm. b.d.	..	2 Gm.	..	..	..	3	..	Expired.
17	44 yr.	18 days	..	Int.	F., Semiconsciousness	N. R. ; K.	+	..	½ Gm. b.d.	30 mg. dly.	4 Gm. I. M. 180 mg. I. T.	..	..	..	6	..	Expired.
18	1 yr.	17 days	..	Int.	C., F., Unconsciousness	N.R. ; Kgs+	+	..	¼ Gm. b.d.	10 mg. dly. 10 mg. alt. dy.	9.5 Gm. I. M. 160 mg. I. T.	1 Gm. b.d.	..	..	23	..	Improvement Grade I.
19	8 yr.	18 mth.	..	Adv.		N. R. Kg's +		..	½Gm. b.d.		1 Gm. I.M.	..	..	..	4	..	Expired.
20	1½ yr.	1 mth.	..	Int.	C., F., Unconsciousness	N. R.	+	..	¼ Gm. b.d.	15 mg. dly. later alt. ds. then 2/week	10 Gm. I. M. 120 mg. I. T.	1 Gm. dly.	60 Gm.	..	80	..	Clinically Improved. Grade I.
21	21 yr.	10 days	MTB	Int.	H., V., F.	N.R. ; Kg's+	+	..	½ Gm. q.d.s.	40 mg.	80 Gm. I. M. 520 mg. I. T.	2 Gm. t.d.s.	..	..	62	..	Clinically Improved. C.S.F. Slight change. Grade I.
22	18 yr.	1 mth.	..	Int.	H., F., Unconsciousness	N. R.	+	..	¼ Gm. b.d.	30 mg. dly. later alt. days	25 Gm. I. M. 480 mg. I. T.	1 Gm. 5 times a day	150 Gm.	..	25	80	Clinically Improved C.S.F. Slight changes After 80 days follow up Pt. all right. Grade I.
23	43 yr.	1 mth.	MTB	Int.	H., F., Unconsciousness	N. R. P.E.	+	..	½ Gm. b.d.	50 mg. dly. later alt. days. 1/wk.	30 Gm. I. M. 400 mg. I. T.	1 Gm. D. S.	28 Gm.	..	28	8	Not Improved. Expired 8 days after discharge.

TABLE 15.—*Case Reports*—(*Contd.*)

Case	Age	Duration of illness prior to adm.	Evidence of TB else where	Stage	Symptoms.	Signs.	Investigations		Treatment.					Adjuvants.	Ped. of obs. in days in		Results.
							Chemistry	Smear	Streptomycin			PAS					
									IM.	IT.	Total	Daily.	Total.		Hosp.	after dis.	
24	34 yr.	8 days	Abd.	Int.	H., V., F. Unconscious	N.R. ; Kg's+ P. E.	+	..	½ Gm. b.d.	50 mg. dly. later alt. days	90 Gm. in 45 days 700 mg. in 35 days	1 Gm. q.d.s.	120 Gm.	..	98	..	Improved. C.S.F. slight Grade I.
25	3 yr.	21 days	Inft. Rt. apex	Int.	H., V., F. Unconscious	N.R.	+	..	¼ Gm. b.d.	20 mg. dly. alt. day 2/ week	40 Gm. in 80 days I.M. 880 mg. I.T.	..	..	..	106	..	Clinically improved C.S.F. practically normal Grade I.
26	2 yr.	1 mth.	Let Lym	Int.		Fever Unconscious	+	.. ..	⅛ Gm. b.d.	..	5/4 Gm. in 5 days.	..	..	..	5	..	Expired.
27	1¾ yr.	3 mth.	..	Int.	F. Unconscious	N.R. ;Kg's + P.E.	+	..	½ Gm. b.d.	15 mg. daily.	2½ Gm. in 5 days I.M. 95 mg.I.T.	½ Gm. b.d.	..	..	5	..	Expired.
28	¼ yr.	25 days	hazinsse left base	Adv.	V., F.	N. R.; Pupils reacting sluggishly	+	..	1/6 Gm. b.d.	20 mg. daily	2/3 Gm. in 2 days	1 Gm.	..	..	3	..	Expired.
29	1½ yr.	15 days		Adv.	V., C., F., Unconscious	N.R. ; Pupil sluggish	+	..	1/6 Gm. b.d.	10 mg. daily	2/3 Gm. I.M. 10mg. I.T.	½ Gm. b.d.	..	..	3	..	Expired.
30	42 yr.	1½ mth.	M.T.B.	Int.	H. V. Unconsciousness		+	..	½ Gm. b.d.	75 mg. 1 /wk.	159 Gm. I. M. 1.7 mg. I. T.	1 Gm. t.d.s.	..	Bom.	6	..	Improved Grade I.
31	9mth.	3 mth.		Int.	F.	N.R. P. E.	+	..	¼ Gm. daily	10 mg. daily alt. days.	7 Gm.I.M. in 28 days 140 mg.I.T. in 14 days	½ Gm. t.d.s.	..	..	28	..	Clinically Improved. Grade I.
32	3½ yr.	2wk.		Adv.	V., F.	P. E.	+	..	¼ Gm. daily	20 mg. daily	30 Gm. I.M. in 70 days 1200 mg. I.T. in 51 days	½ Gm. 4 time	48 Gm.	..	120	..	Improved clinically. C.S.F. showed increase in cells & protein. *Grade I.*

33	5 yr.	22 days	Infiln Left apex	Int.	H., F. Fits	N.R. ; Kg's+		..	¼ Gm. daily	30 mg. daily alt. days thricewk.	42 Gm. I.M. in 82 day 72mg. I. T.	..	27 Gm.	..	82	..	Clinically improved. C.S.F. same. Grade I.
34	2 mth.	1 day	..	Int.	C.		+	..	1/6 Gm. b.d.	..	2 Gm. in 6 days	..	..	..	14	..	Clinically C.S.F. improved. Grade I.
35	6½ mth	22 days	..	Adv.	F. Fits Uncon.	N.R.;Kg's+ Rt. pupil small sluggish	+	..	1/6 Gm. b.d.	10 mg. daily	2 Gm. in 6 days I.M. 20mg. I.T. in 2 day	..	..	..	5	..	Expired.
36	-		..	Int.	V. F.	N. R.	+	..	¼ Gm. once	10 mg. alt. days.	9 Gm. in 36 days I.M. 20mg. I.T. in 2 days	..	..	..	30	..	Not Improved. Grade III.
37	1 yr.	20 days		Adv.	Fits, F. V. Unconscious	N.R.;Kg's+ P.E. Pupils dil. & not acting	+	..	1/6Gm. b.d.	15 mg. alt. days.	15 Gm. I.M. for 45 days 750 mg. I. T.	¾ Gm. daily	27 Gm.	..	5	..	Expired.
38	6 yr.	22 days.		Int.	F. H.	N.R. ; Kg's+		..	¼ Gm. b.d.	..	4 Gm. in 8 days	¾ Gm. daily	..	..	5	..	Expired.
39	5 yr.	15 days.	Cer. Lym.	Int.	F. V. H.	N.R. Pupils dil.	+	..	¼ Gm. b.d.	..	1 Gm. in 2 days.	..	..	..	4	..	Expired
40	2½ yr.	2½ mth.	Infiln Rt. lung	Int.	Fever	N. R.	+	..	1/6 Gm. b.d.	20 mg. daily	28 Gm. I.M. 1180 mg. I. T.	1 Gm. b.d.	..	..	90	..	Improved C.S.F. protein & cell + Grade I.
41	9mth.	13 days		Int.	C. F.	N. R.	+	..	¼ Gm. b.d.	15 mg. daily	27 Gm. I. M. in 54 day 576 mg. I.T.	½ Gm. b.d.	..	..	67	..	Improved. Grade I.
42	2 yr.	21 days		Int.	Unconsciousness	N. R.	+	..	1/6 Gm. b.d.	15 mg. daily alt. dose & so on.	70 Gm. I.M. 720 mg. I.T.	½ Gm. b.d.	..	..	185	..	Improved clinically C.S.F. protein & cells +. Grade I.
43	21yr.	6 wk.	Pl. Rt. side.	Early	Cough F. Pain in Rt. Iliac fossa H.	..	+	..	¼ Gm. b.d.	50 mg. I.T.	128 Gm. in 128 days 715 mg. 15 injc.	1 Gm. q.d.s.	..	..	180	..	Improved C.S.F. normal. Grade I.

F—Fever. C—Convulsions. H—Headache. V—Vomiting. N. R.—Neck Rigidity. Kg's—Kernigs sign. P.E.—Plantar Extensor. Int.—Intermediate. Adv.—Advance. M. T. B.—Miliary Tuberculosis. Cer. Lym.—Cervical Lymphadenitis. Pl. Rt.—Pleurisy Rightside.

with streptomycin and PAS where streptomycin is given both intramuscularly and intrathecally. We feel that the method of administration of intrathecal and intramuscular streptomycin, followed in the present series, seems to be highly satisfactory.

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His Excellency the Governor of Madras will inaugurate the Conference. All medical men interested in pediatrics are cordially invited to participate in the Conference.

Further information may be had from the Secretary General, Prof. S. T. Achar, Department of Pediatrics, General Hospital, Madras.

ORIGINAL ARTICLE

TREATMENT OF HYPERTENSION WITH HEXAMETHONIUM BROMIDE*

H. L. Khosla † and A. Das-Gupta ‡

It has often been said of hypertension that the patient and not the high blood pressure should be treated. Of course in ignorance of definite etiological factors, one is inclined to follow general therapeutic measures, and this accounts for a number of platitudes as regards high blood pressure. Further it has also been established that these patients only seek treatment when certain symptoms are present. One starts wondering what is the treatment in this condition in the absecne of definite etiological factors. Is it the administration of drugs or the restriction of diet? Should one make a point of giving instruction regarding regulating the activity of the patient or insist on the abstinence from stimulants ? Should all these factors be given attention ? Inspite of this, at one or the other stage, the disease usually takes the course of confronting its victims and their relatives, sooner or later, with calamities like cerebral hemorrhage, heart failure, renal diseases and other manifestations. Hay has mentioned that no one can afford to be indifferent to the problems associated with variations in blood pressure, as high blood pressure is an abnormality which always requires investigations, supervision, and careful looking after. Every one who has the disease should try to get rid of it or reduce it just as does a patient with glycosuria. The disasters brought about by persistent glycosuria are quite common with people who neglect it. Similarly, disasters brought about by high blood pressure are no less great. A victim of this, therefore, needs not only management of the disease, but should learn to regulate and learn to control the habits which precipitate the dangers.

A number of drugs have been tried from time to time for producing a sustained fall in blood pressure but none has been really successful. As to the various lines of treatment—potassium thiocyanate, surgical sympathectomy and Kempner's diet,—views are still divided. Suddenly by chance, anesthesists like Hunter and others, working with deca methonium anesthesia, found that the hexamethonium salt, improved the respiratory exchange, especially when it had been depressed and patients were dying of anoxia. Further, it was noticed by them that the other outstanding action of these drugs was the paralysis of autonomic ganglia. Its administration during anesthesia, caused a fall in blood pressure which was quickly restored by an injection of adrenaline or ephedrine. This was also supported by others working with these salts. There was a race amongst these workers to find a synthetic substitute for curare. Paton and Zaimis's exhaustive researches on pharmacological actions showed that compounds with carbon chains of intermediate length (five or six atoms) exert their action at ganglionic synapses rather than at the neuromuscular junction, and that they are capable of profoundly influencing the functions of the autonomic nervous system. This provided an opportunity for a new approach to the management of diseases, in which a hyperactivity of the autonomic nervous system might be concerned, without undergoing any major operation like surgical sympathectomy. Thus various physicians in the West, like Turner and others, termed the treatment with these salts as medical sympathectomy. Arnold and Rosenheim tried these drugs and found that they are effective in producing a reduction in blood pressure in normal and hypertensive individuals. Further, Paton and Zaimis showed that they are stable and soluble and are apparently absorbed freely unchanged from the alimentary tract. As soon as an adequate amount became available, Kay and Smith's work on peptic ulcer showed that hexamethonium bromide is pharmacologically active when given by mouth. This stimulated trials in all possible diseases, where the activity of autonomic nervous system was found to be pathological.

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Restall and Smirk carried out various preliminary tests with the drugs, as to the effect of these drugs on the blood pressure in hypertensive and normal people and indicated good results. Saville, Campbell and Robertson published reports on the use of penta and hexamethonium salts. Some of them were not able to give definite conclusions. But Saville, Campbell and Robertson were hopeful that these drugs would find an important place in the treatment of hypertension. Both of them used large doses. Restall and Smirk reported results similar to those of Campbell and his co-worker in respect of relief from such manifestations as headache and breathlessness.

MODE OF ADMINISTRATION

Further difficulty came regarding the mode of administration of the drugs. Each worker has his own method and so far no standard methods have been established. Smirk claimed effective blood pressure reduction with subcutaneous injections of penta and hexamethonium bromide which led to a clinical improvement in severe hypertensives which was of a higher order than that ordinarily obtained by other methods. The results obtained by oral therapy were much less reliable, though sometimes good. Turner had similar results and cited favourable experience in toxemic and other hypertensions of pregnancy. Frankel preferred hexamethonium bromide to other drugs and regarded intramuscular injection as more effective than the oral dosages.

Locket who mainly used oral therapy with hexamethonium bromide regarded the results as unsatisfactory, whereas Mackay and Shaw concluded that they had remarkable results with oral therapy. The advantages of these new methods of management of hypertensives are obvious. The principal disadvantages appear to be, first, that the daily dosage of the drug, necessary to produce a useful effect, varies greatly from patient to patient, and secondly, the effective dose is separated from the disabling dose by an increment which is only fractional.

The benefit, on the other hand, has been similar to the findings of the other workers, which has been due to the lowering of blood pressure and relief of symptoms. Smirk tried these drugs in 150 cases of varied etiology; benign, essential, fixed, labile and after sympathectomy cases, and malignant. The modes of administration he used and found most effective is the subcutaneous, though he tried oral, intramuscular and intravenous routes besides the subcutaneous one. Further, during the course of the treatment they have gone from one route to the other without important subjective changes being apparent to the patient. To prolong the action of the drug, it was used in almond oil suspension mixed with 1 in 400,000 to 1 to 100,000 adrenaline hydrochloride. He started with small dosages, subcutaneously, 15-25 mg, till tolerance is obtained and slowly increased the quantity to obtain the required and desired blood pressure. In the early period of the treatment some unpleasant symptoms like faintness, dizziness, may occur which can be obviated by giving a little adrenaline or administering the drug in an almond oil suspension. The injection is given with the patient in sitting posture and the blood pressure is taken every 15 to 20 minutes. Thereafter the dose is gradually increased with injection given 3 times a day. After a few weeks, a dose of 200 to 250 mg. will produce a constant effect . Assessing the result of each dose has to be decided by trial in every case.

Whereas Locket adopted the intramuscular route beginning with 25 mg. and then watching the blood pressure for two hours and if this dose was not sufficient he increased the dose by 20 mg. and repeated the procedure until a satisfactory fall in blood pressure was obtained. The drug was repeated six hourly as tolerance was increased, and interval was increased until in some cases the dose was as much as 100 mg. three hourly. After a couple of weeks the drug was given by mouth, about 200 mg. six hourly. All this was started after some rest in bed and the patients were treated as out-patients.

Mackay and Shaw used this drug by mouth, starting with 0.25 Gm. tablets, crushed and dissolved in water, before meals. The commencing dose was 0.25 Gm. three times a day. This was increased to the maximum tolerable dose. In an average case, the dosage was stabilized at approximately 0.5 Gm., thrice daily, before meals.

In the present investigation we followed the oral method starting with 0.25 Gm. thrice daily, and thereafter 0.5 Gm. every four hours and also, in some cases, 50 mg. by subcutaneous injection every six hours, four times a day. We apologise for the small number of cases and regret to say that it has not been due to the dearth of cases but due to a shortage of medicine. We had a very limited amount of the drug which lasted only for these few cases.

CASE REPORTS

Case 1. S. R. S., aged 51, a Hindu male, an officer, was admitted on 29-8-51 for giddiness, headache, palpitation, and dyspnea on exertion for the last 6 months. His high blood pressure was detected five years back in a casual examination when he used to have no symptoms. His blood pressure on admission was 200/150; pulse full and bounding, no signs of cardiac failure. The left ventricle was enlarged, which was coroborated on radiographic examination which further revealed an uncoiling of the aorta. No bruit was heard anywhere. The aortic second sound was booming. No signs of pulmonary congestion were present. Fundus examination revealed thickening and spasm of the arteries (Grade I, Keith and Wagner's classification,) Urine—No albumin, no sugar. Kidney function tests were normal. Blood Urea—45 mg. per 100 cc. Electrocardiogram showed left axis deviation with inversion of T waves in lead II.

For two weeks he was put on (i) light diet (salt free, rice diet), (ii) phenobarbitone ½ gr. b.d. without much effect. He was then given hexamethonium bromide orally, 1 tablet or 0.25 Gm., three times a day, with the diet already mentioned. Gradually the dosage was raised to 2 tablets or 0.5 Gm., every four hours, 5 times a day. With gradual increase of dosage, tolerance was observed without any toxic symptoms. The general condition of the patient improved within a fortnight of the beginning of the treatment. Giddiness, headache and palpitation decreased and the dyspnea

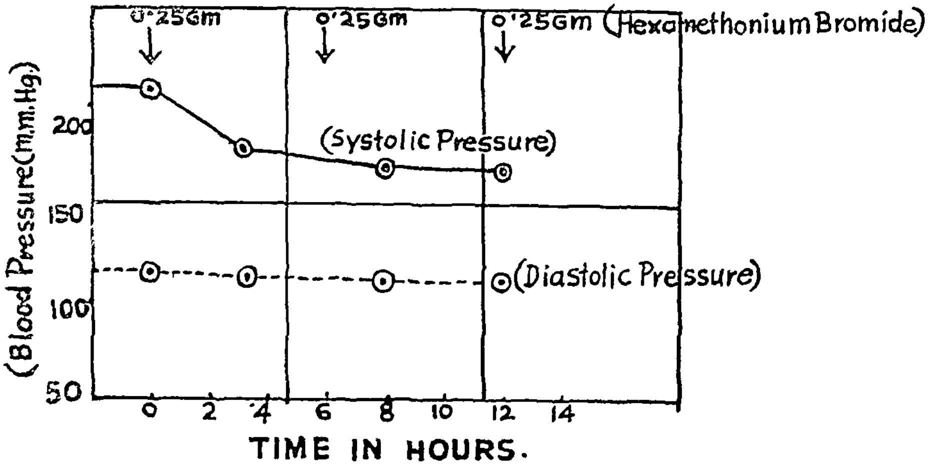

Fig. 1.—Shows the effect of hexamethonium bromide 0.25 Gm. thrice daily on B.P.

was much less. His pressure fell after 15 days of treatment to 160/120 to 140/115. A month later he became capable of light exercise without dyspnea and was discharged on a maintenance dosage of 0.25 mg., three times a day.

We noticed in this patient that the total stoppage of salt in the diet caused an appearance of the toxic symptoms of bromide. Side effects were minimum. Occasionally he used to complain of dizziness on going to the bath room. This was the result of postural hypotension. He complained very often of frequent constipation, a dry mouth and loss of appetite.

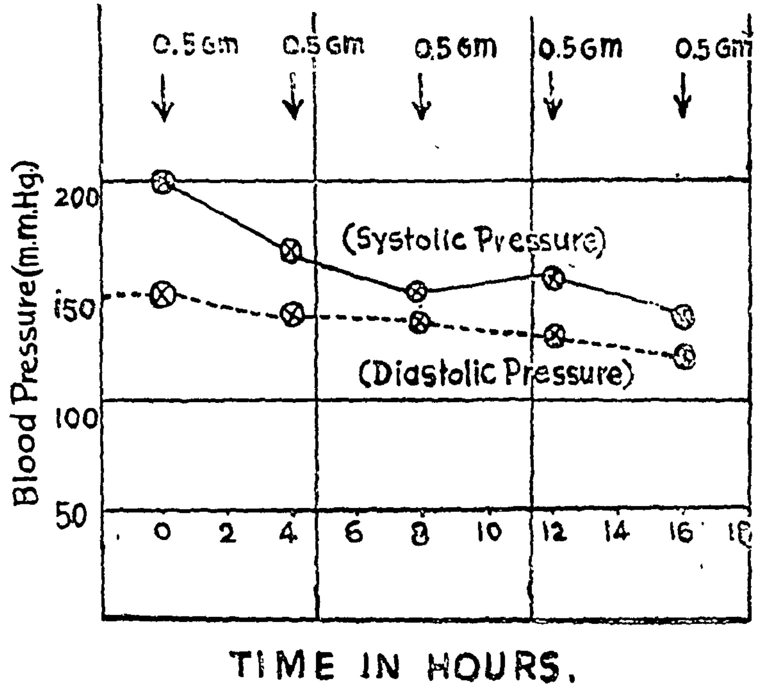

Fig. 2.—Shows the effect of hexamethonium bromide 0.5 Gm. every four hours 5 times a day on B. P.

After discharge on a salt free diet he felt rather severe symptoms of bromism. He was quickly put on a salt diet and felt better.

Case 2. Mr. C., aged 55, a Hindu, was a man of worrying disposition and had a previous history of giddiness and a reeling sensation on walking. He said he could not concentrate on his work for the last six months and used to get a very disturbed sleep at night. His wife said that he very often talked incoherently and passed sleepless nights. Last year he had an attack of brisk epistaxis. His blood pressure on examination was 212/115; pulse 80/min; respiration—18/min. No signs of congestive failure were present. No clinical enlargement of the heart was seen. The heart sounds were normal and no murmurs were heard in any of the cardiac areas. There was no lung congestion. Ophthalmoscopic examination revealed arteriosclerotic changes with ripping of the veins at the arterio venous junctions. (Grade II, Keith and Wagner). Urine—Sp. Gr. 1022, no sugar, no albumin. Urea 86 mg. on admission. Preliminary treatment with sedatives like phenobarbitone ½ gr. twice daily and a mixture containing pot. bromide and chloral hydrate, 15 gr. each, thrice daily, had very little effect on the blood pressure. He was then tried with 0.25 Gm. hexamethonium bromide orally, three times a day, along with a modified Kempner's diet as in the first case.

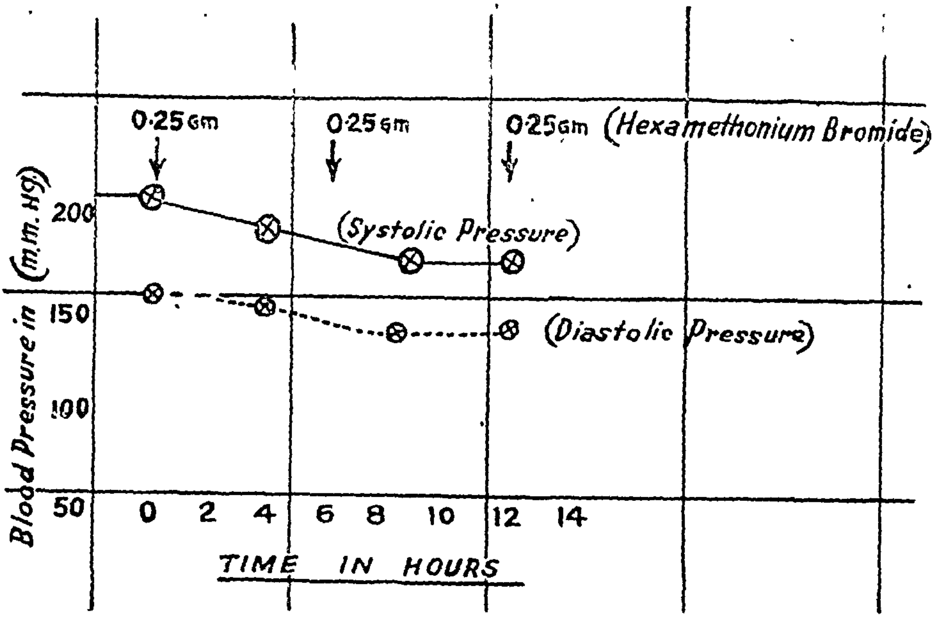

Fig. 3.—Shows the effect of hexamethonium bromide 0.25 Gm., three times a day.

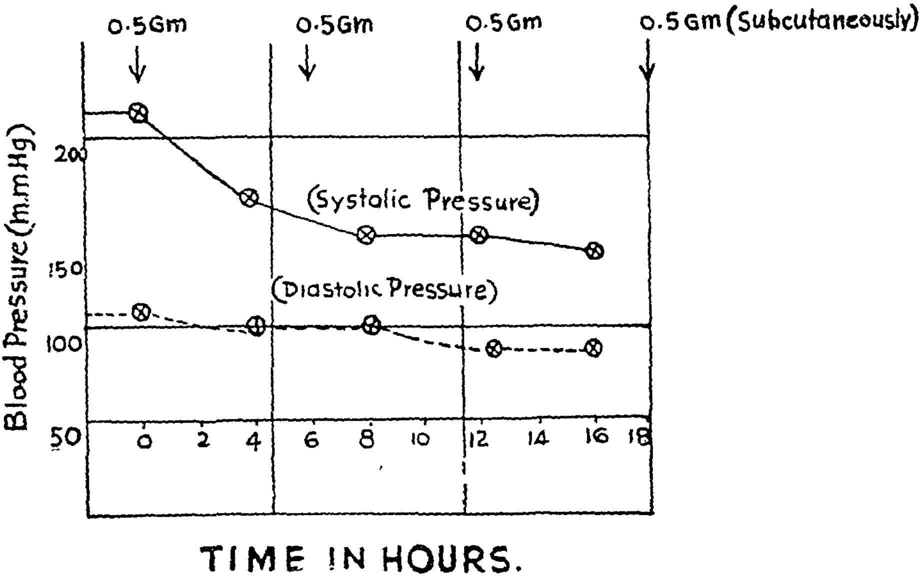

Fig. 4.—Shows the effect of hexamethonium bromide 0.5 Gm. every 6 hours. (subcutaneously).

Although the blood pressure showed a slight downward trend he had very little amelioration of symptoms. In this case, without trying any further heavier oral dosage, we started with 20 mg. hexamethonium bromide by subcutaneous injection, and gradually increased to 50 mg., every 6 hours, four times a day. Before the administration of hexamethonium bromide, he was very boisterous and very often used to talk irrelevantly but with the injections, the blood pressure came down to normal and was maintained by six hourly injections. His general symptoms of headache, giddiness, *etc.*, became better within one week. Subjective untoward effects like dryness of the mouth, blurring of vision, nocturnal incontinence were complained of. These symptoms, however, did not last long. After one month of treatment he had no symptoms and was discharged from the hospital, on a maintenance dose of 0.25 Gm. t.d.s.

Case 3. L. B. R., aged 50, was admitted on 26-9-1951 with malignant hypertension and diabetes and his blood pressure was found to be 190/100 on admission. The symptoms were of five months duration, and were giddiness, headache, tiredness, dyspnea on exertion, cardiac asthma, and dimness of vision. He also used to have insomnia very often and could not sleep for nights together. The family history revealed diabetes in the other members of the family. His condition deteriorated rather much within a few weeks before admission to the Medical College Hospital.

On examination he was moderately built, with signs of left ventricular failure. The left ventricle was enlarged. A systolic murmur in the aortic and mitral areas was present. Pre-systolic triple rhythm was present at the apex. An accentuated second sound at the pulmonary area and pulmonary congestion was present. The liver and spleen were not palpable. Roentgenograms revealed enlargement of left ventricle, the uncoiling of the aorta and evidence of pulmonary edema. The electrocardiogram with standard leads showed left axis deviation, regular rhythm, and no evidence of any block. Urine examination showed no albumin, sugar—a trace, Sp. Gr.—1010, reaction—alkaline, hyaline and granular casts, and a few red blood cells were present. Blood urea on admission was 86 mg. per 100 cc. Blood sugar—145 mg. per 100 cc. Urea concentration test showed much impairment on admission. Ophthalmoscopic examination showed papilledema, flame shaped hemorrhages near the discs in both eyes, shiny exudates on the temporal side of the Rt. eye, and deep hemorrhages in the lower part of left side of the disc of the left eye (Grade IV Keith and Wagner).

He was given hexamethonium orally 0.5 Gm., every four hours along with 2000 calories diabetic diet and insulin, 10 units b.d. His sugar was controlled. Although his blood pressure came down and his headache and dyspnea were relieved, his general condition did not improve. Later, he developed signs of uremia and finally died inspite of the treatment. No toxic symptoms were revealed.

Case 4. R. P. D., aged 48, was admitted for giddiness, dyspnea on exertion, dimness of vision and retrosternal discomfort on 2-1-52. On examination, he was a well built person with a blood pressure of 190/110 on admission. There were no signs of cardiac failure. Pupils were reacting to light, reflexes were normal. The left ventricle was enlarged. No murmur was heard in any of the cardiac areas. The lungs showed hyperemia. X-ray revealed enlargement of the left ventricle and uncoiling of the aorta.

Urine—Sp. Gr. 1020, sugar and albumin were not present. Urea—50 mg. per 100 cc. Urea concentration test was normal. Electrocardiogram showed left axis deviation. Eye grounds revealed evidence of arteriosclerotic changes, development of exudates and hemorrhages but no papilledema. The patient was put on a salt poor, rice diet, and phenobarbitone ½ gr. twice daily. *Rawolfia Serpentina* 1 t. d. s. for seven days without much clinical improvement.

Hexamethonium bromide was given orally, 2 tablets *i.e.*, 0.5 Gm. every four hours, five times a day. Within fifteen days of treatment, his vision improved, headache, dyspnea and retrosternal pain disappeared. Blood urea and the renal function tests were unaltered. Exudates in the eye grounds were absorbed after a further months' stay in the hospital. He was discharged on a maintenance dosage of 0.25 Gm. hexamethonium bromide, 3 times a day. He felt well and was symptom-free.

TABLE 1.—*Synopsis of Cases.*

	Complaints.	Eye Gr. on Adm.	Maintenance dose.	Subjective change.	Eye gr. after treatment.	Objective change.	Toxic symptoms.
M. 51.	Giddiness, Palpitation, Headache, Dyspnea.	Grade I. Keith & Wagner.	0.25 Gm. T.D.	Improved.	Grade I.	B.P. Lowered.	Constipation. Dryness of mouth. Mental confusion.
C. 55.	Giddiness, Lack of concentration, Insomnia.	Grade II.	0.25 Gm. T.D.	Improved.	Grade II.	B.P. Lowered.	Dryness of mouth. Blurring of vision. Nocturnal incontinence.
L.B.R. 50.	Dyspnea, Cardiac Asthma, Dimness of vision.	Grade IV	....	Slight improvement	Grade III.	B.P. Lowered.	Nil.
R.P.D. 48.	Giddiness, Dyspnea,. Retrosternal pain.	Grade II.	0.25 Gm. T.D.	Improved.	Grade II.	B.P. lowered.	Nil.
A. 45.	Headache, Dyspnea	Grade I.	0.25 Gm. T.D.	Improved.	Grade I.	B.P. lowered.	Nil.

Grade: I. Spasm of the arteries, and thickening of the arteries.
,, II. Grade I plus nicking of the veins at arteriovenous junction.
,, III. Exudates plus flame shaped hemorrhages.
,, IV. Grade three plus papilledema.

Case 5. A Parsee male, aged 45, complained of headache and dyspnea on heavy exertion. The blood pressure on admission was 170/120. Pulse, 95/min., regular. The heart showed no enlargement and no signs of failure. The aortic second sound was accentuated. X-ray of heart was normal. The electrocardiogram was normal. Blood urea—35 mg. per 100 cc. Urine—Sp. Gr. 1015, was alkaline in reaction, with no sugar and no albumin. The urea concentration test was normal.

He was given 2 tablets of hexamethonium bromide (0.25 Gm.), every four hours. There was a relief of symptoms within 7 days of treatment. The average blood pressure measurement after 7 days was 145/110. He was given a maintenance dosage of 0.25 Gm. t.d.s. and discharged.

DISCUSSION

It has been stated recently that the benefits to be derived from methonium salts in hypertension are uncertain, and that there is no strong indication that their introduction has changed the outlook for patients with high blood pressure. Our findings and results do not agree with these. Reports of many other workers leave no room for doubt that these compounds are the most powerful hypertensive agents, yet developed. Unfortunately, the main draw-back has been that the effective dose is often uncomfortably close to that which will do harm and the right dose has to be discovered for each case. As to the modes of administration there is still a difference of opinion—Professor Smirk advocates the subcutaneous injection. We agree with him that in urgent cases subcutaneous injections should be started and then gradually be replaced by oral administration; as seen, there have been side effects due to postural hypotension or blocking of the autonomic ganglia, which include faintness, dizziness or syncope, dryness of the mouth, anorexia, nause a abdominal distension, constipation and mistiness of vision. The effect of the postural symptoms are averted by avoiding standing still for any length of time, and can be countered by using an abdominal binder or adrenaline and ephedrine. With the continuous use of the drug the ill effects tend to become less troublesome. Rosenheim has observed that the low salt diet during the treatment with these drugs is liable to produce bromism. In our cases we noticed a patient who went on a complete salt free diet without our instructions and soon he was brought to the hospital with mental confusion and high blood bromide. The intake of salt was immediately increased and the drug was stopped for the time being. The patient recovered speedily. More investigations and work are indicated on this aspect.

In this series, the cases treated were those of malignant hypertension, hypertensive encephalopathy and hypertension with renal damage. Clinical examination, roentgenogram, electrocardiogram, blood urea, renal function and fundus examination were carried on admission and before administering the drug and thereafter, at regular intervals, to see the effect of the drug. The blood pressure of patients treated with the drug falls very dramatically, but tends to show variations in level even in the course of the day. The variations in systolic pressure are much greater than those of the diastolic pressure. The postural changes have a great effect on the production of hypotension. In most of the cases, after a fortnight's treatment, the blood pressure came to a stationary low level.

Other symptoms, like headache and dyspnea, were relieved in all of the cases and patients felt better immediately the treatment was started.

Improvement in the cardiac condition has been assessed by clinical signs, symptoms, radiological examination and electrocardiography. All cases were relieved of dyspnea, palpitation and symptoms, which were the main cause of admission to the hospital.

Renal function has been mostly normal and after several months of treatment with these drugs there have been no appreciable change or deterioration of renal function.

Eye ground changes are :—

1. Exudative phenomena where there were hemorrhages, edema and with the improvement of the blood pressure, this condition disappeared.

2. Narrowing, hardening, tortuousity of the arteries—no effect of the improvement in blood pressure was seen at all.

It is obvious that prolonged study of many cases will be necessary before conclusions can be drawn regarding the degree and duration of hypertension necessary to reverse retinopathy.

SUMMARY

1. The advantages and usefulness of the drug in the treatment of high blood pressure are obvious and it relieves unpleasant symptoms and the patient feels better at once.

2. It certainly is not the cure, but keeps the blood pressure in check and within harmless limits and a useful measure of control.

3. Administration of the drug by the oral method is good and gives good results, but recourse to subcutaneous injections should be started in severe cases and thereafter replaced by oral administration.

4. The disadvantage is the daily dosages necessary to produce useful effects varies from patient to patient.

5. Untoward side effects like giddiness, dimness of vision, nausea, vomiting and constipation were observed in some cases. In one case, symptoms of bromism appeared by keeping the patient on a prolonged salt free diet which however disappeared by giving him more salt in his diet and withdrawing the drug immediately.

Further work is required in various spheres of the drug so as to standardise the dosages and modes of administration.

ACKNOWLEDGMENT

We are thankful to May and Baker, London, for supplying us with hexamethonium bromide for oral and subcutaneous injections, and also to the House-physicians who helped us in carrying out these investigations.

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UNDILUTED BONE MARROW STUDIES IN HEALTH AND DISEASE †

D. Govinda Reddy *

A number of modifications of bone marrow aspiration technique have been recommended, since the method was originally introduced by Arinkin[1]. Many investigators have realised that the aspirated material is not a true representative of bone marrow, as the aspirated fluid happens to be a mixture of bone marrow particles and peripheral blood. Thus, the gross appearance and the total nucleated count of the aspirated fluid is not a reliable estimate of the bone marrow cellularity. Various authors found wide variations in the total nucleated counts among normal individuals and even among several counts performed upon different samples of the same aspirate. This has resulted in conflicting descriptions of normal and abnormal marrows. To overcome this, improved methods in the study of aspirated marrow have been suggested from time to time. Chief among them are (1) concentration of marrow cells by mixing the aspirate with an anti-coagulant (heparin) and centrifuging the mixture and examining the deposit, and (2) smears and imprints of solid marrow particles selected from the aspirate. A good marrow particle smear has a very near approach to the true marrow architecture seen in a section ; but unfortunately, marrow fragments are not present always. Robert S. Fadam and Irving Berlin[10] have compared the differentials obtained from particle smears and from random sample smears of the same aspirate in 50 cases and found that smears made from aspirate particles represent more accurately a bone marrow, than do those made from random samples of the aspirate fluid. Regrettably, in several instances, they had to perform multiple aspirations to obtain marrow particles. Even surgical trephine biopsy had to be undertaken in instances, where repeated marrow aspirations have failed to yield marrow cells or particles of diagnostic value.

I have devised a new sternal puncture needle with the help of which it is possible to obtain bone marrow from the sternum, undiluted with blood. A description of the needle and the technique employed was published[9]. The advantages of examination of marrow thus obtained were pointed out in that article. Since then, this technique was extensively used in the wards of the General Hospital, Madras, and the advantages originally claimed were substantiated. The use of this needle was demonstrated by the author, at the 77th Meeting of the Pathological Society of Great Britain and Ireland, held at London in January 1949.

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† Paper read at the Annual Conference of the Association of Pathologists of India, at Hyderabad in November 1951.

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The present communication is a preliminary note on the personal observations of the author, in the study of bone marrow in normal health and a few select pathological conditions.

I. NORMAL MARROW

For this, the marrow was obtained from the sterni of 8 young men admitted for the surgical treatment of inguinal hernia. They were otherwise healthy and their blood hemoglobin and cell counts were normal. Smears made from the marrow, showed sheets of cells with their anatomical relations undisturbed (Fig. 1) and differential counts disclosed a consistently greater percentage of immature cells of the granulocytic and erythrocytic series, than did those from the aspirated material. Megaloblasts were never met with. Certain difficulties were encountered in the preparation and staining of the marrow particle smears. The smears are greasy due to the presence of fat and the cells do not get stained to the same intensity as in the case of aspirated marrow cells. However, there is no hindrance to identification and enumeration of the cells.

II. PROTOZOAL AND BACTERIAL INFECTIONS

(1) *Malaria* :—Seyfarth and Lucrezi[12] state that the marrow contains more parasites than the peripheral blood. Schoch found that plasmodia were not more numerous in the marrow than in the blood. My personal experience is in agreement with the latter author. A careful examination of the peripheral blood including thick drop examination will always show the parasite and a positive finding in the marrow smear is rare, where the parasite is not found in the peripheral blood. Crescents, when seen in the marrow, are also to be found in the peripheral blood. Hemozoin pigment, also, is not conspicuous in the marrow, whereas the spleen pulp smears invariably show the pigment.

(2) *Kala-azar* :—The experience in kala-azar definitely shows the superiority of examination of marrow removed by this technique. Several fields and sometimes several slides made from the aspirated material have to be examined to find Leishman Donovan bodies. In smears made from the undiluted marrow, numerous parasitised cells are found unruptured (Fig. 2), thus saving time in the search for the parasites. There are occasions where Leishman Donovan bodies are found in the spleen pulp, where the smears made from the aspirated bone marrow were negative for the parasite ; but no such instance has occurred when the undiluted marrow was examined. Thus examination of undiluted marrow smears are as good, if not superior to spleen pulp smears, in the diagnosis of kala-azar.

(3) *Leprosy* :—Lepra bacilli are abundant in the bone marrows in lepromatous leprosy. An attempt was made to examine the sternal marrow of apparently healthy children in contact with lepers. The author has an idea that the bacillus having gained entrance into the body of contact children, multiplies in the reticuloendothelial system of the marrow of the contact children and later during adolescence gets disseminated to the cutaneous structures. Unfortunately, due to lack of co-operation from the parents, a sufficient number of examinations could not be carried out and it is hoped to pursue this investigation to demonstrate the bacillus in the marrow long before the appearance of clinical manifestations of leprosy.

III. ANEMIAS AND LEUKEMIAS

(1) *Nutritional Macrocytic Anemia* :(*Tropical Macrocytic Anemia*): The bone marrow changes are variable in this condition. A megaloblastic reaction indistinguishable from a true case of pernicious anemia is not at all unusual. In a large number of cases that I have examined, the marrow showed a mixture of megaloblastic and normoblastic reaction. Trowell[13] named these cases " dimorphic anemia ". Here there is a deficiency of both liver factor and iron. Since we know that megaloblastic marrow may exist in a number of clinical conditions, in which the liver principle may, in some manner or other, be ultimately denied to the bone marrow, the differentiation of pernicious anemia from nutritional macrocytic anemia should not rest with the examination of marrow only, but should take into account other important clinical findings, such as the state of gastric acidity, associated neurological manifestations, Van den Bergh reaction and response to liver therapy. In a very large series of cases of anemia that I have investigated among South Indians, I have found only a few cases of true Addisonian pernicious anemia. While it is true that pernicious anemia is not unknown in the tropics, the diagnosis must be established by all possible means before it can be accepted, a point very well brought out by Das Gupta and Chatterjea[3].

A review of the literature on the subject of macrocytic anemia in association with hepatic cirrhosis reveals diversity of opinions. In a series of 132 patients, with various types of hepatic involvement, Wintrobe[14] has noticed the presence of macrocytic anemia in 21.9 per cent of cases. The genesis of megaloblastosis in association with cirrhosis of the liver is ascribed to deficiency of the erythrocytic maturation factor stored by the liver. The evidence in support of this hypothesis has been lacking or, at least, contradictory. Movitt[7] has seen megaloblasts in the sternal marrow in 3 cases in a series of 30 patients with cirrhosis of the liver. Leitner, Britton and Newmark[5] have seen them only in one case. In a small series of cases, examined by me, I have failed to see even once, a true megaloblastic picture in the bone marrow. In my

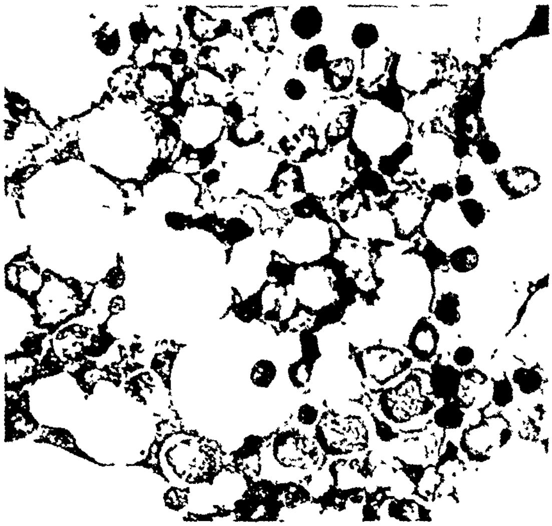

Fig. 1.—Photomicrograph of normal marrow smear showing sheets of cells with their anatomical relations undisturbed. x 800.

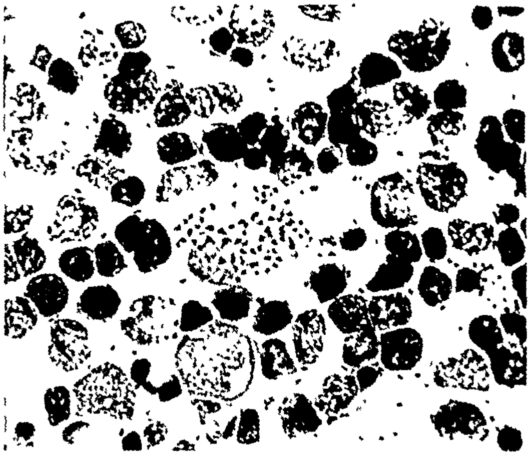

Fig. 2.—Photomicrograph of bone marrow smear from a case of kala-azar. Marrow cells are found in large numbers with very few erythrocytes. One large monocyte loaded with Leishman-Donovan bodies is seen. x 1000.

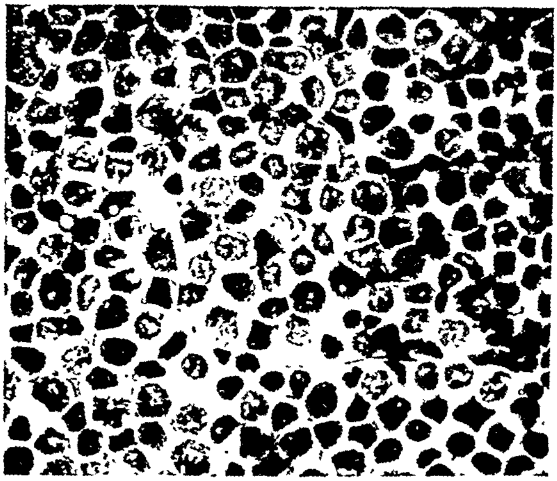

Fig. 3.—Photomicrograph of marrow smear made with undiluted bone marrow in lymphatic leukemia. Lymphocytes are found in sheets resembling a sectioned leukemic lymph node. x 1000.

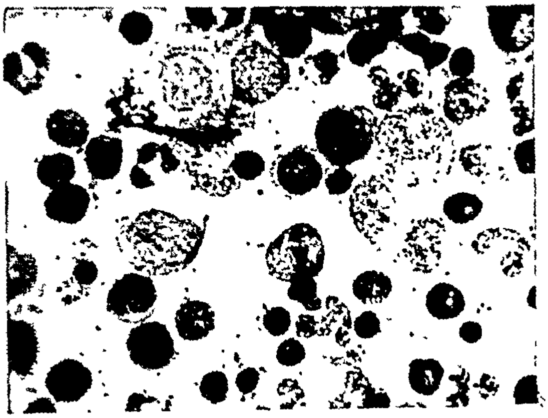

Fig. 4.—Photomicrograph of bone marrow smear, from a case of Hodgkin's disease. Note the large sized monocyte. Sternberg giant cells were not present. x 1100.

opinion, several cases reported in the medical literature are examples of nutritional factor deficiency anemias, in persons with cirrhosis, rather than the macrocytic anemias of chronic liver disease. The need for confirming the diagnosis of cirrhosis of the liver by liver biopsy cannot be ignored.

(2) *Lymphatic Leukemia* :—Sternal puncture is a valuable aid to diagnosis in lymphatic leukemia, since even in the early stage of the disease, it will show definitely a moderate increase of lymphocytes with a few atypical forms. Still one should remember, that during aspiration, occasionally a lymph follicle may be aspirated and then the smear may contain mainly lymphocytes leading to a mistaken diagnosis of lymphatic leukemia or lymphosarcoma. There is divided opinion about the marrow changes in chronic lymphatic leukemia. Doubt has been expressed whether the entire bone marrow gets involved in lymphoid hyperplasia. Aspirated bone marrow shows a preponderance of lymphocytes but there is always an admixture of other cells. But, smears made with undiluted bone marrow showed sheets of lymphocytes (Fig.3) resembling a sectioned lymph node in lymphatic leukemia. Evidently, aggregations of proliferated lymphocytes are not easily mobilised from the parent tissue during aspiration.

IV. NEOPLASTIC CONDITIONS

(1) *Hodgkin's Disease* :—Sternal puncture shows the specific finding of Sternberg cells in lymphadenoma only rarely. Dresser[4] described frequent involvement of the sternum. But Marchal *et al.*[6] in a series of 42 cases found bony involvement 6 times, and 3 of these in the sternum. In a series of 6 cases examined by this technique, typical Sternberg cells were not seen even once ; but a good number of very large sized monocytes were conspicuous (Fig. 4). Rohr and Heggalin[11] described similar cells and thought they were Sternberg giant cells. Dameshek[2] observed an increase of histiocytes up to 24 per cent. The significance of these large sized monocytes requires further investigation.

(2) *Multiple Myeloma* :—It is often mentioned that this condition can be diagnosed on the basis of a study of the aspirated marrow, even when roentgen findings are negative. Plasma cells, when present even in small numbers, are considered sufficiently abnormal to permit a diagnosis. Two cases have come under the observation of the author. In the first one, the diagnosis was confirmed by biopsy examination of bone marrow from the primary site in the ileum. Later multiple lesions developed, ending in death. Both in this case and another, which is under observation, plasma cells were not seen in the sternal and vertebral marrow even after repeated examinations.

V. LIPOID STORAGE DISEASES

Gaucher's Disease:—In the literature there are excellent reports of the presence of characteristic storage cells of Gaucher in the bone marrow. It is considered by some that the involvement of the skeletal system is as constant in Gaucher's disease as the involvement of the spleen. Pittalug and Rof[8] failed to find any specific changes in the sternal marrow but found them in splenic puncture. Only one case of Gaucher's disease came under my care. The diagnosis was primarily made from the spleen puncture and later confirmed from the histological sections made from the resected spleen. Repeated punctures of the sternal bone marrow failed to show Gaucher's cells.

SUMMARY

Reference is made to an improved method of obtaining bone marrow undiluted with blood. Smears made with the marrow obtained with the new needle were found superior to those of aspirated material and even aspirated particle smears. Some observations in the study of bone marrow in normal health and a few select pathological conditions are described.

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THE ANTIHISTAMINE DRUGS

F. P. Antia * and J. N. Sidhva

From the time that Sir Thomas Lewis[19] first associated histamine with the production of the urticarial rash, the search for drugs to antagonize or neutralize its effect in the body has progressed, till today, a large number of synthetic anti-histamine preparations are marketed. To appreciate and evaluate the action of these drugs, the action and effects of histamine will have to be considered first.

HISTAMINE

Histamine is chemically related to the amino acid histidine, and is actually histidine with a carboxyl group removed. Dale and Laidlaw[9] were the first to describe and analyse its effects in various animals. They ascribed the following actions to histamine :—

1. Contraction of smooth muscle especially of the bronchioles, uterus and intestines.
2. A fall in the blood pressure in most species, including man. This is due to arteriolar dilatation. In some species (notably the rodents), the arterioles are constricted and a rise in blood pressure results.
3. Dilatation and increased permeability of capillaries with exudation into the tissue spaces.
4. Increased secretion of various glands, notably the gastric. Lewis[19], on pricking histamine into the skin, noticed the 'Triple Response' consisting of :—
    - (*i*) A red line 3-4 mm. in diameter, due to capillary dilatation.
    - (*ii*) A flare 2-3 cm. in diameter, due to arteriolar dilatation.
    - (*iii*) A wheal, due to exudation of fluid.

Since these are the effects produced in the skin on the local introduction of the appropriate protein in patients subject to urticaria, it was assumed that the reaction to the protein was due to the action of an 'H-substance' (histamine-like substance). From this, and from the fact that the effects observed by Dale and Laidlaw in animals on administration of

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histamine were identical with those seen in animals in anaphylactic shock, it was concluded that histamine was the most potent chemical initiator of the anaphylactic reaction.

The present-day view as regards the production of the anaphylactic reaction is expressed by Dale[8], as follows :—

The normal antigen-antibody reaction occurs in the blood or tissue fluids, resulting in immunity. When this reaction takes place with the antibodies attached to the fixed tissue cells, these cells are damaged, resulting in the liberation of histamine, which gives rise to the anaphylactic reaction. The variable distribution of the antibodies in the different organs accounts for the diverse manifestations of the anaphylactic response in different species. This theory is supported by the fact that histamine can be extracted from various tissues, suggesting that it might exist in some bound, physiologically inactive, state, and be set free by an agent injurious to the tissues, producing the anaphylactic reaction(Best *et al.*[2]).

INTRINSIC AND EXTRINSIC HISTAMINE

Dale[8] has divided histamine into two categories 'intrinsic' and 'extrinsic'. Intrinsic histamine acts on the very cells which produce it, *e. g.*, the anaphylactic response of the muscles of the bronchioles, uterus or intestines.

Extrinsic histamine, on the other hand, is produced by certain cells and acts on others remote from its site of production, *e. g.*, the vascular responses of the skin and nasal mucosa, where the histamine is released in the epidermis or naso-pharyngeal epithelium and diffuses to the subjacent vascular plexus.

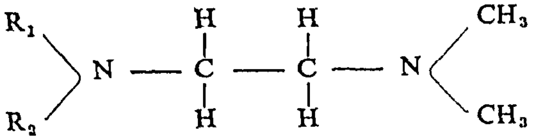
Just as atropine acts better against 'extrinsic' acetylcholine (injected) than against 'intrinsic' acetylcholine (liberated at the cholinergic nerve-endings) so also the antihistamine drugs are supposed to act better against extrinsic than intrinsic histamine.

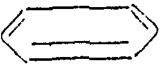
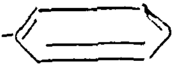
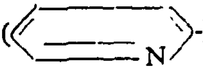
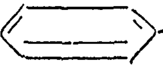
This might perhaps explain why the anti-histamine drugs are so much more effective in urticaria, hay-fever and vasomotor rhinitis (extrinsic histamine) than in spasmodic asthma (intrinsic histamine).

CHEMISTRY OF THE ANTIHISTAMINE DRUGS

The chemistry of the earlier antihistamines (with the exception of thephorin) is based on the general formula "di-methyl-ethylene-diamine." Antergen, anthisan, pyribenzamine and histadyl conform to this general formula. Benadryl, antistin and phenergan though similar to this formula, progressively differ from it. Other drugs like thephorin have no similarity to the ethylene diamine formula at all.

General Formula—Dimethyl-ethylenediamine



In the case of antergan and pyribenzamine, R$_1$ is the benzyl (CH$_2$-) group whereas in the case of anthisan it is the p-methyoxy-benzyl (CH$_3$ O-CH$_2$-) group. R$_2$ in the case of anthisan and pyribenzamine is the 2-pyridyl (-) group and in the case of antergan it is the phenyl (-) group.

More recently Loew and Micetich[20] and Stone and Loew have described a new series of compounds having the general formula:—N-(2-haloalkyl)-1-naphthalenemethylamine. Of these, N-(2-Chlorethyl)-N-ethyl-1-naphthalenemethylamine is the most important member. It is said to be as potent as anthisan both in antihistamine and anti-anaphylactic actions as seen by experiments on the guinea pig.

EVALUATION OF THE RELATIVE POTENCIES OF THE VARIOUS ANTIHISTAMINES

Two methods have been described to determine the relative potencies of various antihistamine drugs.

The first, described by Friedlaender *et al.*[11], employs the lethal dosage method, using guinea pigs. They gave 3 mg./Kg. of the antihistamine drug intraperitoneally. Fifteen minutes later they determined the minimum number of L. D. 100 doses of histamine, given intravenously, to prove fatal to the guinea pigs under observation. Their results were as follows :—

Drugs.	Dosage required.
Benadryl	5 doses
Antergan	6 doses
Pyribenzamine	37 doses
Anthisan	125 doses

Halpern[13] using 10-20 mg./Kg. found that phenergan protected guinea-pigs even upto 1500 L.D. 100 doses of histamine. In his experiments, anthisan in the same dose of 10-20 mg./Kg. protected guinea-pigs against 400 L. D. doses of histamine.

The second method, employed by Bain *et al.* utilises the property of inhibition of the histamine wheal by antihistamine substances. They measured the amount of drug necessary to reduce the area of histamine-produced wheals by 50 per cent, and thus compared the weight for weight potencies of the various drugs. Since phenergan was found to be by far the most potent and the longest acting drug, they employed it as a standard for comparing the potencies of the other antihistamine drugs. They expressed the relative weight-for-weight potencies of the various antihistamines in terms of a ratio, the "Mean Potency Quotient," (M. P. Q.). The M. P. Q. of a given antihistamine drug is :—

$$\frac{\text{Mean dose of drug for mean antihistamine effect}}{\text{Mean dose of phenergan to produce the same effect}}$$

It signifies the number of times phenergan is more potent than the drug under consideration. The higher the M.P.Q. of a given drug the less potent it is. The M.P.Q. of anthisan is about 7 and that of antistin about 15.

This method has also been employed by Bain *et al.* to estimate the duration of action of the various drugs. They first administered the drug to be tested and at regular intervals induced histamine wheals. These were naturally inhibited in direct ratio to the degrees of action still retained by the antihistamine drugs. The time taken for the loss of potency of the drug from full action to half action was noted. The times for different drugs were recorded as follows :—

Phenergan	19½	hours.
Anthisan	5	hours 10 mins.
Antistin	3½	hours.
Pyribenzamine	3¼	hours.

The relative duration of action of the various drugs was also expressed in the form of a ratio, the "Mean Duration Quotient" (M.D.Q.). The M.D.Q. of a particular anti-histamine is:—

$$\frac{\text{Time for maximum to } \tfrac{1}{2}\text{-maximum action for phenergan.}}{\text{Corresponding time for approximately equi-effective dose of drug.}}$$

It expresses the half-action time of phenergan as a multiple of the half-action time of the drug under consideration. The higher the M.D.Q. of a drug the shorter its duration of action. The M.D.Q. of anthisan is 3.8 and antistin 5.6.

Similarly Bain *et al*[1]., have expressed the relative therapeutic efficacy of the various antihistamines in chronic urticaria in terms of the "Mean Therapeutic Quotient", (M.T.Q.). The M.T.Q. of a drug is:—

$$\frac{\text{The daily dose of the drug.}}{\text{The daily dose of phenergan to produce an equal therapeutic response.}}$$

It expresses how many times phenergan is therapeutically more efficacious in chronic urticaria than the drug under consideration. The M.T.Q. of a drug therefore varies inversely as its therapeutic efficacy. The M.T.Q. of anthisan in chronic urticaria is about 14.

The discrepancy in the values of M.T.Q. and M.P.Q. for anthisan serves to illustrate the difference between the therapeutic efficacy of an antihistaminic drug and its potency as measured experimentally in animals, or by inhibition of the histaminic wheal in experiments on human subjects. This difference in the therapeutic and experimental potency of the antihistamines may be due to the fact that they possess atropine-like, quinidine-like, local anesthetic, soporific, analgesic and other actions. These actions may be beneficial in some cases and detrimental in others, thus enhancing or lessening the therapeutic effect of the drugs.

MODE OF ACTION OF ANTIHISTAMINE DRUGS

The present-day concept of the mode of action of the antihistamine drugs is that of " substrate competition". It is postulated that the antihistaminics combine with a hypothetical specific receptor substance in the cells and thus prevent it from combining with histamine. This serves to explain why these drugs can merely neutralise the effects of histamine *in vivo*, and yet, can neither chemically neutralise histamine *in vitro*, nor exert pharmacologically opposite or antagonistic actions in the body in the absence of histamine. This further seems to support Dale's hypothesis of intrinsic and extrinsic histamine. Though ordinary concentrations of the drug are required to combine with receptors and thus exclude the histamine liberated elsewhere, greater concentration of the drugs would be required to prevent histamine from combining with the receptors of the cells which actually produce it.

For the theory of " substrate competition " to hold water, the antihistamine should bear a chemical similarity to histamine (to explain the affinity of both substances for the same chemical receptor). In the case of certain drugs, like anthisan, similarity in part of the formula is marked. With benadryl it is much less so, and with thephorin it is practically non-existent. These substances should also be able to protect histamine from histaminase. Whereas some drugs, like antistin, do possess this action, others like anthisan do not.

Therefore, it appears that the mode of action of the antihistamine drugs is probably more than just a simple substitution of histamine by the antihistamine drugs in the specific receptor of the cells.

ACTIONS OF ANTIHISTAMINE DRUGS

The action of the antihistamine drugs may be divided into two main groups :—

A—Antihistamine actions proper.

B—Other actions.

A—Antihistamine Actions—The drugs can neutralise or nullify all the actions of histamine with the exception of that on gastric secretion. They cannot act on normal mechanisms or mechanisms deranged by means other than by histamine, with perhaps the exception of phenergan which actively diminishes capillary permeability by some direct means (Halpern[15]).

The actions of histamine that are counteracted by these drugs are :—

1. *Spasm of Involuntary Muscle* :—In this case pyribenzamine, anthisan, and phenergan are much more effective than antistin, antergan or benadryl. This action of antagonism, by anthisan, of muscle spasm induced by histamine, has been employed to identify histamine in tissue extracts, just as atropine helps in the identification of acetylcholine.

2. *Lowering of Blood-Pressure* :—This can also be prevented as shown in experiments on anesthetized cats or dogs.

3. *Increase of Capillary Permeability* :—Antihistamine drugs have been shown to antagonise this effect by diminishing or preventing the

escape of an intravenously injected dye, trypan blue, into the tissues at the site of intradermal injection of histamine. The direct action of phenergan in diminishing capillary permeability has already been referred to.

4. *The Histamine Wheal* :—The inhibition of the histamine wheal, by the antihistamine drugs has been used by Bain *et al*[1]. for estimating the relative potencies of the various antihistaminic drugs.

5. *Gastric Secretion* :—The stimulation of gastric juice secretion is the only action of histamine not antagonised by the antihistamine drugs. They may, in fact, actually increase the secretion of hydrochloric acid in certain species. This is strikingly seen in the work of Halpern,[13],[14] who showed that although guinea pigs could be protected against the immediate effects of 1500 times the L. D. 100 doses of histamine, many animals died 24-48 hours later with acute perforations of the stomach, probably due to the excessive amount of hydrochloric acid secreted by the gastric mucosa, due to the powerful stimulus of the massive dose of histamine.

B—Other Actions :

1. *On the Central Nervous System* :—Most of the drugs, especially benadryl, produce a mild sedation. Hewer and Keele[19] have demonstrated the analgesic action of anthisan and benadryl and this is the probable explanation of the relief they produce in some patients with pruritus. On the other hand, some drugs like thephorin produce stimulation, leading to insomnia.

2. *Local Anesthetic Action* :—All the antihistamine drugs have a local anesthetic action. For example, anthisan is found to be about three times as potent as procaine (Dews and Graham,[10])

3. *Quinidine-like Action*—Anthisan has been found to be twice as effective as quinidine in prolonging the refractory period of the rabbit's atrium (Dews and Graham,[10]).

4. *Anti-Adrenaline Action* :—This action is seen in the newer anti-histamine drugs like N-(2-chloroethyl)-N-ethyl-1-naphthalenemethylamine (Loew and Micetich[20]). A theory was once advanced that the antihistaminic drugs acted by liberating adrenaline from the suprarenal medulla, which then antagonised the actions of histamine, but the anti-adrenaline action of some of the antihistamines disproves it.

5. *Anti-Acetylcholine Action* :—These drugs produce an atropine-like effect on smooth muscle, glands, *etc.* but Schild[29] has shown, that for this a rather high concentration is required, which is not reached by therapeutic doses necessary to antagonise histamine. Anthisan is most specific in this respect, its anti-acetylcholine action being very weak.

ADMINISTRATION AND DOSAGE

The antihistamine drugs are usually given by mouth as tablets, capsules or as elixirs to children. Occasionally they may be given by subcutaneous, intramuscular or slow intravenous injection, although parenteral administration has no real advantage over the oral route.

By the oral route the drugs are absorbed quickly and reach peak levels in the blood in 1½ to 4 hours. Although it is said that the effect of a single dose does not last for more than six hours, Bain *et al.*[1] have shown that phenergan has a more prolonged effect. Phenergan is therefore administered by them in a single dose at night. The side effects are negligible during the night and pass off before the morning whereas the therapeutic action is much more prolonged, lasting over 24 hours. The other antihistamines have to be given three or four times daily, and since they cause increased motility of the alimentary tract and (with the exception of benadryl) produce nausea on an empty stomach, they are best given after meals. The usual adult dosage of the various antihistamine drugs is as follows :—

Drug.	Dosage in mg.	Max. dose in mg. in 24 hours.
Phenergan, Thephorin	25	150-200
Benadryl, Pyribenzamine, Histadyl.	50	400
Antistin, Anthisan	100	800

This dosage also applies to children over 12 years of age.

For younger children, Britton[4] recommends starting with 1 teaspoonful (4 cc.) of the elixir available (anthisan, benadryl or pyribenzamine). This is about 1/5th to 1/4th the adult dosage. This dose is then progressively increased till a therapeutic effect is obtained or side-effects preclude its further administration.

CLINICAL USES

It has already been shown that the results of experimental studies on the potencies of antihistamines are no guide to their effectiveness in clinical use. This is one of the factors to be taken into account when choosing an antihistamine drug, and the physician should not be swayed by encouraging results in experimental studies on animals unless they are backed up by corresponding results in clinical application.

Another, perhaps more important, consideration is that no two patients will react in exactly the same way to a given antihistamine drug, and as such, the therapeutic effectiveness and the frequency and severity of side effects will vary quite a lot with different patients. It is therefore advisable that one drug after another should be tried out to see which one is best suited to the patient.

Finally, it should be borne in mind that the antihistamine drugs are merely palliative and only histamine antagonists in the body. They are not a ' cure ' for allergic conditions and as such they are in no way substitutes for desensitization procedures, nor do they replace adjuvants to therapy like the antispasmodics or expectorants in asthma.

Urticaria and Angioneurotic Edema :—In these conditions about 80 per cent of the patients are reported to obtain considerable relief from the antihistamine drugs. The acute forms respond well, and the relief of itching is more marked than the diminution of the edema. In emergencies like edema of the glottis or swelling of the tongue, adrenaline is necessary. The antihistamines can be given to prevent recurrence.

Hay Fever :—About 70-80 per cent of the patients are reported to experience excellent relief from the antihistamine drugs. In hay fever, pyribenzamine and anthisan appear to be more effective than benadryl or antistin.

Serum Sickness :—In this condition administration of the antihistamine drugs does not shorten the course but ameliorates the symptoms to a certain degree. The skin and mucous membrane manifestations are much more responsive to these drugs than are the joint symptoms.

Vasomotor Rhinitis :—About 50 per cent of the patients get symptomatic improvement, the relief of sneezing and itching being more marked than the reduction of intra-nasal edema. For this reason it may be desirable in some cases to add vasoconstrictor drugs like ephedrine to the antihistamine preparation.

Asthma :—The response of this condition to antihistamine drugs has been extremely disappointing. Earlier clinical studies suggested that these drugs might be of some value in the control of asthmatic states. For instance, McGavack *et al.*[21] reported very encouraging results by using a single large dose of antihistamines in the early stages of asthmatic attacks. Most workers, however, did not find this method useful. In fact many of them think the antihistamines may be actully harmful to asthmatics. Ratner[23] goes so far as to say that the antihistamines are capable of causing suffocation by drying up bronchial secretions, and may prove extremely harmful in patients in *status asthmaticus*. Britton[4] also considers the antihistamines as practically valueless in the treatment of bronchial asthma. He only recommends the use of benadryl in mild nocturnal asthmatic attacks, and even here he gives more importance to the sedative side-effect of benadryl than to its antihistamine effect.

Herxheimer[16], however, reports better results from a study of normal and asthmatic subjects in whom bronchial obstruction and bronchial asthma were induced by the inhalation of histamine, mecholyl and allergenic extracts, and the protective effect of the antihistamines was studied. He found that mild bronchial obstruction and spasm could be prevented by the previous administration of phenergan or anthisan, though no such protection was achieved when the asthmatic attack induced was severe. He recommends the administration of antihistamines at night combined with ephedrine by day, superimposed acute attacks being controlled by aleudrin (isopropylepinephrine). He claims very good results in a number of patients treated by him in this manner.

Until there is proof of better and more efficacious remedies for the treatment of bronchial asthma, the schedule recommended by Herxheimer seems to be the most effective method of dealing with this problem.

The lack of response to the antihistamines in bronchial asthma can be explained by Dale's theory of intrinsic and extrinsic histamine, the intrinsic histamine acting on the bronchial muscle being much more refractory to the action of the antihistamines than the extrinsic variety which is responsible for the production of urticaria, vasomotor rhinitis and hay-fever.

NON-ALLERGIC CONDITIONS

1. *Parkinsonism* :—The beneficial effects of these drugs in Parkinsonism was practically confined to diminution of rigidity, the tremor being unaffected (Ryan and Wood,[26].)

2. *Motion Sickness* :—One of the antihistamine drugs, " dramamine," has been demonstrated to have striking effects on sea-sickness (Gay and Carliner,[12]). In an experiment carried out on a troopship, 372 out of 389 (about 95.6%) soldiers experienced complete relief in one hour following the oral administration of " dramamine". Its effects are found to be less on airsickness. In the original experiment on the troop-ship no side effects were reported, but Britton[1] rather vaguely says that " from personal experience........the side-reactions may be worse than the seasickness".

3. *The Common Cold* :—In 1947, Brewster[5] first reported the ameliorating effect of diphenhydramine hydrochloride (benadryl) in 10 per cent of cases of the common cold. In a later series he described extremely good results in 90 per cent of patients treated within an hour of onset of symptoms and 74 per cent of those treated within six hours.

Unfortunately, other workers have not been able to confirm these early favourable reports. Paton *et al.*[22] for example, in trials with anthisan, did not get any appreciable results. Similarly, Hoagland *et al.*[18] working with pyribenzamine and chlorothen reported the same disappointing results. They agreed with Brewster in that the subjective symptoms were relieved to a certain extent by the antihistamines, but they attributed this to the fact that these drugs lessened the serous nasal discharge.

In a report of the Council on Pharmacy and Chemistry of the American Medical Association,[7] the literature on this subject is reviewed. It pointed out a number of discrepancies in the reports where the validity of diagnosis and cure was left to the patients. More than half of the series had either inadequate controls or no controls at all. Thus the interpretation of results were open to question. They also put forward suggestions for a scientific study of these drugs on the common cold. Till such time as a scientific study is carried out, the effect of antihistamine drugs on the common cold remains in doubt.

SIDE ACTIONS AND TOXICITY

The side actions of these drugs vary more from patient to patient than from drug to drug in comparable dosage. Some of these side-actions, like drowsiness with benadryl, can be turned to advantage, in treating urticaria at night, or nocturnal asthma in children.

Drowsiness and lassitude are the commonest side-effects seen most with benadryl, (which can be combined with 5 mg. of amphetamine to counteract this effect), and least with thephorin, which actually produces insomnia.

Other side-effects like nausea, vomiting, colic and diarrhea can be avoided by giving the drugs after meals.

Britton[1] gives the following list of side-effects which may be seen during therapy with the antihistamine drugs in order of frequency: drowsiness, dizziness, weakness, nervousness and mental incoordination, nausea, headache, diarrhea, tinnitus, vomiting, irritability, dryness of the mouth, and tachycardia.

There is no evidence to suggest that tolerance is developed to these drugs on prolonged administration. So far, no toxic effects on the kidney, liver or blood have been noticed, with the exception of one case of granulocytopenia with pyribenzamine (Blanton and Owens,[3]).

Accidental overdosage with antihistamine has proved fatal in children. Rives *et al.*[24] have described the case of a child of 16 months who took 100 mg. of thenylene hydrochloride. After initial depression of the central nervous system, convulsions occurred. On autopsy, cerebral edema and upper nephron nephrosis were observed.

SUMMARY

The antihistaminic drugs are an important addition to the symptomatic therapy of allergic diseases. They are more effective in urticaria, hay-fever and vasomotor rhinitis than in spasmodic asthma. The relative efficacy and side-actions of the drugs vary from patient to patient and, therefore, it is advisable to start with a small dose and at a time

when the patient is not called upon to do any skilled work. Finally, it must again be stressed that the antihistamine drugs are only palliative or preventive, and not a cure for allergic diseases. Desensitization procedures should be undertaken wherever necessary.

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Do you know that ! ! !

Correlation coefficients of vital capacity, complemental air, reserve air of the lungs diminish and the functional residual air and residual air increase in proportion to smoking. The ratio of residual air to the total lung volume increases also. These changes are reversible when the smoking is given up.

Smoking produces diminution in chest expansion. Abstracts of World Medicine, **10** : 349, 1951.

Do you know that ! ! !

In left-handed children the time of dentition, of walking, and of speech development is normal. The development of intellect is the same as that in right-handed children. Thirty per cent of left-handed children are born in abnormal way. Nail-biting, speech disturbances, character disturbances and bed-wetting are more common in left-handed children. In 23 per cent of left-handed children there is a left-handedness in the family. Parents of 30 per cent of such children are alcohol addicts and 46 per cent of such parents are mentally disturbed. Abstracts of World Medicine, **10**: 376, 1951.

As to fashion, in a disease in which the prognosis is inevitably fatal and which may appear suddenly and unexpectedly in the dearly loved only child of a family, irrespective of wealth or social status, it is inevitable that, like the Athenians, there should always be a searching after "some new thing". At a certain level of society there will be a demand for the very latest treatment, such as may be found to be fully documented or at least optimistically described in some lay publications, which know that advances in medicine are news, long before they have been either properly tested or confidently advocated in the medical press. It is as well to keep pace with such fashions, since a display of knowledge about them and even their employment may be one of the ways in which the morale of the household may be maintained. B. M. J. **2**: 1572, 1951.

ISONICOTINIC ACID HYDRAZIDE (ISONIAZID) IN TUBERCULOSIS

AN INTRODUCTORY REVIEW

C. J. Modi *

" When Ehrlich discovered the specific treponemacidal action of salvarsan, he drew aside the curtain of uncertainty and set free a search, still vigorous, for anti-bacterial agents of all kinds. Just as it was appropriate that Pasteur's discovery of antibiotics eventually developed into a vast armamentarium of antibiotic agents, it is appropriate that the discovery heralded here is a relatively simple organic salt".

" The systemic ravages of the tuberculous process are halted...... with a rapidity, a certainty and to a degree which we have never observed in other chemotherapeutic or antibiotic agents". (Robitzek, Selikoff and Ornstein[13]).

It seems we are on the threshold of a new era in the treatment of tuberculosis. Squibb and Hoffman-La Roche Chemists have independently discovered a new drug, isonicotinic acid hydrazide ; other drug houses are likely to introduce new drugs in the treatment of tuberculosis.

Waksman's discovery of streptomycin in 1945 has been hailed as the greatest single advance in the treatment of tuberculosis. Then followed promizole and PAS. However, these drugs have their own shortcomings particularly seen in prolonged treatments The neurotoxicity of streptomycin and gastro-intestinal upsets of PAS are well known. Accordingly, research laboratories all over the world continued their search for a less toxic, less costly drug that could be used to destroy the tubercle bacillus.

In Germany, a compound known as tibione had been used with encouraging results in tuberculosis. It belonged to a group of compounds known as thiosemicarbazones. It was too toxic. Following this clue, research workers tested hundreds of thiosemicarbazones, reasoning that some that were less toxic might have been overlooked. The supposition proved correct and nydrazid and rimifon turned up in the Squibb and Hoffman-La Roche Laboratories almost simultaneously. The drug is a hydrazide of isonicotinic acid. Here was Science's most amazing coincidence. Two research groups, working independently, discovered the same drug simultaneously[8]. This reminds us of the discovery of vitamin B_{12} by Rickes and Lester Smith, the two separated by the Atlantic.

Isonicotinic acid hydrazide is not a new chemical. Two German chemists, H. Meyer and J. Mally, had already synthesized it as far back as 1912. However, its medical worth was not known and the world

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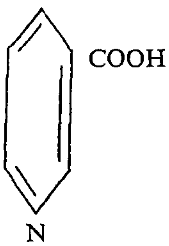
had to wait for nearly forty years before its amazing action against tuberculosis was demonstrated.

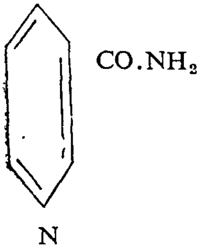
As the name indicates, the drug is related to nicotinic acid, one of the vitamin B complex factors. Let us study the closely similar chemical structure :

(1)



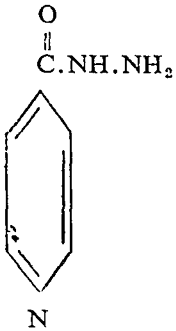
Nicotinic Acid

(2)



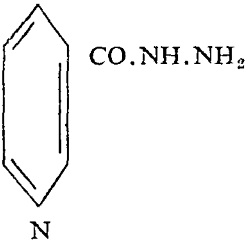
Nicotinic
Acid Amide

(3)



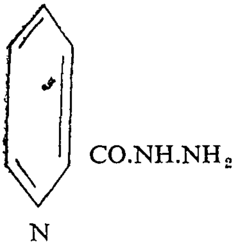
Isonicotinic Acid Hydrazide (4-pyridine carboxylic acid hydrazide)
(Nydrazid—Squibb)
(Rimifon — Roche.)

(4)



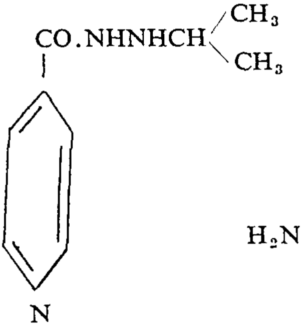
Nicotinic Acid Hydrazide
(3-pyridine carboxylic acid hydrazide)

(5)



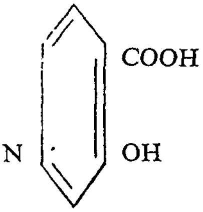
Picolinic Acid Hydrazide
(2-pyridine carboxylic acid hydrazide)

(6)



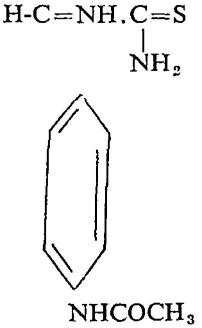
MARSILID-Roche
Isonicotinyl-
isopropyl hydrazine.

(7)



Para - amino
Salicylic Acid

(8)



Tibione paraacetamido-benzaldehyde thiosemicarbazone.

It is amazing that it is only isonicotinic acid hydrazide that possesses the specific action against mycobacterium tuberculosis. The alpha product is only half as active and the beta product is inactive against tuberculosis. The isopropyl derivative (marsilid-Roche) is equally effective, while the glycosyl derivative is less important. The drug is so simple, any chemist can achieve the synthesis.

Isonicotinic acid hydrazide (isoniazid) is a white, crystalline powder available in tablet form for the oral treatment of tuberculosis. It is freely soluble in water at any pH. It is poorly soluble in the common inert organic solvents such as ethanol, ether and benzene. Dry, and in neutral and acid aqueous solutions, it is stable at room temperature.

ABSORPTION [5]

Isoniazid is almost completely absorbed from the digestive tract. The early peak plasma drug-levels obtained with oral administration to dogs were essentially the same as those achieved by intravenous administration.

The similarity of $L.D._{50}$ values in mice when either of the hydrazides (rimifon or marsilid) was administered by several routes points to the completeness of absorption of these compounds in mice.

DISTRIBUTION [5]

After a single oral dose of the drug, 3 mg./Kg. body wt., peak plasma concentrations between 1.3 and 3.4 μ/Gm. per cc. are reached within one to six hours in most patients. (The minimum inhibitory concentration of isonicotinic acid hydrazide against the BCG strain of mycobacterium tuberculosis is 0.02 μ/Gm. per cc. It is thus seen that a blood level, 60 to 170 times the minimum inhibitory concentration against tubercle bacilli, is easily reached even after a single oral dose of 3 mg./Kg. body weight.

Thereafter the concentration falls, until little or none of the drug can be detected by the method used (Kelly and Poet[9]) after 24 hours. Renal clearance studies indicated the presence of significant amounts of the drug in the plasma at the twenty-fourth hour.

Patients receiving 1.5 mg. per Kg. twice daily, had plasma concentrations of 0.6 to 1.4 μ/Gm. per cc. Three hours after the last dose (30 to 70 times the minimum inhibitory concentration) and the drug could still be detected in the plasma seven hours after the last dose. Repeated determinations made three hours after the last dose showed no consistent change in the plasma concentration during five weeks of medication. Thus there is no evidence of cumulation or the development of tolerance to the drug[5].

Mice were fed on diets containing nydrazid 2, 8, 32 and 126 times the minimum effective level. At intervals upto 17 days, mice were sacrificed, and pooled blood samples were submitted for drug analysis. In no instance was a concentration of drug exceeding 5.56 μGm./cc. in plasma obtained[12].

Similarly, two mongrel dogs were utilized for plasma determina tions of hydrazid after single oral doses of .4 and 20 mg./Kg. and one intravenous dose of 5 mg./Kg. Rapid absorption after oral dosage was indicated since peak plasma drug levels were attained in 30 minutes or less. At the end of 5 hours the plasma drug level was at least 33 per cent of the one hour level[12].

Salivary concentrations roughly parallel the plasma concentration of the drug. Isonicotinic acid hydrazide passes freely into the cerebrospinal fluid. Patients without meningitis receiving 1.5 mg. per Kg. twice daily, had concentrations of 0.5 to 0.55 μ/Gm. per cc. of cerebrospinal fluid. Patients with tuberculous meningitis receiving 2 to 3 mg. per Kg. twice daily had concentrations of 1.77 to 4.10 μ /Gm. per cc. [5].

It has been shown that the amount of the drug present in plasma, pleural exudates and cerebrospinal fluid is all fully active. From the above, it is clear that the concentrations of isoniazid obtained in the body fluids far exceed those registered to control the tubercle bacilli [5].

EXCRETION[5].

Isoniazid is excreted largely into the urine. After a single oral dose of 3 mg. per Kg., 47 to 70 per cent of the total dose appears in the urine within 24 hours. At most, only 5 to 10 per cent of an ingested dose appears in the feces within 24 hours.

ANTI-TUBERCULOUS ACTIVITY

In Vitro:—Isoniazid has a remarkably specific action against *Mycobacterium tuberculosis in vitro.* The Bacillus-Calmette-Guerin (BCG) is inhibited in concentrations of 0.02μ /Gm. per cc. A large number of strains of *Mycobacterium tuberculosis*, *Var. hominis*, including freshly isolated strains from patients and of *Var. bovis* were controlled *in vitro* by nydrazid-concentration of 0.032 to 0.06 μ /Gm. per. cc.

Grunberg and Schnitzer[6] found rimifon to be bacteriostatic against *M. tuberculosis* at a concentration of 0.015 μGm./cc. while marsilid was active at 1.5 μGm./cc.[7]. The compound is accordingly weight for weight at least five times as active as streptomycin, which inhibits BCG at a concentration of 0.1 to 2 mg. per cc[4]. Nydrazid is not effective against other general bacteria but it has a slight antifungal activity.

It is effective against *Mycobacterium tuberculosis* resistant to streptomycin or PAS.

Steenken and his colleagues[16] believe that isonicotinic acid hydrazide exhibits greater *in vitro* activity, requiring only 0.02 to 0.05 gamma per cc. for complete inhibition of growth for 14 days as compared to 1.6 to 3.1. gamma per cc. required by marsilid—the isopropyl derivative.

In vitro studies showed that the number of viable units per cc. of culture medium was 25,00,000 at the end of incubation for 5 days in the control flask, while it was less than 10 in the flask containing 10 gamma per cc. of marsilid. This test confirms the marked tuberculocidal effect of the product in *in vitro* studies[16].

RESISTANCE[4]

In vitro, *M. tuberculosis* can be made resistant to isoniazid and such strains are still fully sensitive to streptomycin. There is as yet no evidence that the development of nydrazid resistance is of importance *in vivo*.

In Experimental Animals :—With thiosemicarbazone therapy, viable tubercle bacilli could be recovered from animals treated with these substances even when no gross lesions could be seen. On the contrary, isonicotinic acid hydrazide produces lasting damage to the tubercle bacilli[6].

Grunberg and Schnitzer[6] have carried out extensive standard tests (treatment for 21 days, with autopsy on 22nd day) in mice experimentally injected intravenously and intranasally with *Mycobacterium tuberculosis.* The results clearly demonstrated the striking anti-tuberculous effect exerted by these compounds. They found 50 per cent protective dose (PD_{50}) to be 4.6 mg./Kg. of rimifon and 7.3 mg./Kg. for marsilid in the intravenous infection of mice. In the intra-nasal infections, the corresponding figures were 6.2 mg./Kg. for rimifon and 10.7 mg./Kg. for marsilid.

Thus the hydrazide derivatives of isonicotinic acid are characterised by their protective effect in comparatively small doses in the experimental tuberculosis of mice. This effect moreover was qualitatively different from that of known substances with anti-tubercular activity. The cultures taken from the lungs of protected animals showed that no viable organisms were apparently present in these lungs, at least in certain dosage ranges, while all controls as well as unsuccessfully treated animals showed more or less heavy growth of *M. tuberculosis.* Practically all animals were free of viable tubercle bacilli after the 21st day of treatment with 10.0 mg./Kg. rimifon in the intravenous and intranasal infection and in the case of marsilid, the effect was achieved with 25 mg./Kg.

Identical results were obtained by the above investigators when the drug was administered by stomach tube and by subcutaneous injection once a day. It is thought that the absence of viable organisms at the time of discontinuation of therapy may result in a lasting protection[7].

This unusual activity of isonicotinic acid hydrazide against mycobacterium tuberculosis is a specific one. The drug is not effective in bacterial infection due to the hemolytic streptococcus, pneumococcus, salmonella infections and influenzal viral infections of mice. The specific anti-tuberculous activity compares very favourably with that of other anti-tuberculous drugs. It appears to be about 4 times as effective as streptomycin and 700 times as effective as PAS.

The intranasal infection seemed to respond just as well as the hematogenous injection. From this, the authors conclude that the drug has a tuberculocidal effect *in vivo* and may be expected to act regardless of the route of infection[6]. In a standardised infection of mice with the ravanel strain of *M. tuberculosis*, the minimal effective dose of nydrazid was found to be 1/700 that of PAS[2].

Steenken[16] injected 20 guinea pigs subcutaneously with a standard dose of a definite strength of tubercle bacilli. On the 21st day after infection, treatment with marsilid was commenced, at first intramuscularly, and later orally. Seventy-three days after infection the animals were sacrificed and on autopsy examination, there was very little evidence of tuberculous infection, both macroscopically and microscopically. Some animals, however, still harboured tubercle bacilli. Fifteen guinea pigs were given the infection intra-cerebrally. Of these, 5 were used as control, 5 were treated with tibione and 5 with marsilid. All the control animals died within 25 days of infection and the tibione treated animals died by the 40th day. However, the marsilid treated animals were alive and well 60 days after infection. The tuberculin skin test turned negative. The progress of these five animals is interesting. Four of these have died (30, 38, 41 and 42 days after termination of treatment) and the 5th is showing progressive paralysis of hind quarters. The tubercle bacilli could be recovered from the cervical lymph nodes of these animals.

The rabbits were given tubercle bacilli intravenously in a dose sufficient to kill all of them in three to four weeks. Three weeks after infection, all the control animals developed miliary pulmonary tuberculosis and died, at the most, in 30 days after infection. In the marsilid treated animals, there was no evidence of miliary tuberculosis on roentgenograms. All the animals remained well during the 71 days of treatment. Within 10 weeks of cessation of treatment, the rabbits showed a relapse of tuberculosis.

In the opinion of these authors[16], the dramatic beneficial effects of isopropyl nicotinic acid hydrazide on acute guinea pig tuberculosis surpasses that seen with any other single antibacterial agent except streptomycin.

In Rhesus Monkeys :—Monkeys frequently develop fatal tuberculosis when brought in contact with civilisation. A positive cutaneous test with old tuberculin correctly indicates gross tuberculosis in the majority of these animals. Once infected, death takes place within four to six weeks with generalised tuberculosis. Zieper and Lewis[17] treated a monkey suffering from pulmonary tuberculosis with 10 mg. of isoniazid by mouth for 19 days and 100 mg. daily of the glucosyl derivative intraperitoneally for the next forty days. During this period, the animal recovered rapidly and its weight rose from 2200 to 3200 Gm. Two and a half months after initiating the treatment, the monkey was sacrificed. The histopathological examination of the tissues of the monkey showed a marked inflammatory process in the peribronchial tissues of the lungs characterised by lymphoid infiltration. One large tracheobronchial lymph node was completely destroyed by a necrotizing process and walled off by connective tissue. In none of the inflammatory lesions could tubercle bacilli be demonstrated. A small number of bacilli could, however, be shown in a smear from the pus of the tracheo-bronchial lymph node. No specific pathological changes were found in kidney, liver or spleen, although fatty infiltration was observed in the first two.

Clinical arrest of the tuberculous process in this animal was extraordinary in view of the lack of immunity in monkeys and the unusually rapid course of simian tuberculosis. Postmortem evidence substantiated the diagnosis of tuberculosis and indicated that the action of isonicotinylhydrazine was long lasting. Re-examination of the cultures after 4½ months continued to show no growth of the tubercle bacilli.

TOXICITY IN EXPERIMENTAL ANIMALS

Acute Toxicity :—In 135 albino mice employed for acute toxicity determinations, the acute oral, subcutaneous, and intravenous LD_{50} ± SE were 190 ± 6; 170 ± 5; 165 ± 4, mg./Kg., respectively. The symptoms of toxicity were excitement, prostration, running movements and convulsions. All the animals died within two hours. One unanesthetized dog was given 100 mg./Kg. isoniazid intravenously during a 5-minute period. Thirty minutes later, the animal vomited and had excessive salivation. prostration, and clonic convulsions soon followed. The dog died 75 minutes after the injection. Similar results were obtained in a second dog which was injected 50 mg./Kg. It is about 22 mg./Kg. per day when the dosage was repeated every 24 hours for two weeks.[12]

Steenken's studies[16] in experimental animals have shown that isonicotinic acid hydrazide is well tolerated by the guinea pigs when given in the dosage upto 35 mg. per Kg. per day intramuscularly for 6 weeks.

Given orally, the drug was well tolerated for 2 weeks at a dosage of 40 mg. per Kg. per day. These rabbits tolerated 15 mg. (9 mg. per Kg. per day) twice daily, intramuscularly for 21 days.

Benson and his colleagues[1] have carried out acute toxicity tests in 324 mice. There was little difference in the toxicity of rimifon and marsilid, when given by different routes, though the oral route with marsilid therapy appeared to be slightly less toxic. Large single doses induced signs of central nervous system stimulation terminating in death due to respiratory failure. In mice and dogs, the isopropyl derivative was found to be less toxic than isonicotinic acid hydrazide. Given orally to rats and rabbits, isoniazid was found to be less toxic than the isopropyl compound. Intravenously given to the rabbits, the isopropyl compound was less toxic as compared to isoniazid.

Sub-Acute Oral Toxicity[12] :—5 groups of albino rats, each group consisting of 5 rats, were given varying doses of nydrazid by mouth. It was found that in the rat, a 40 mg./Kg. dose was equivalent to the maximum acceptable dose of 64 mg./Kg./day in the mouse. The symptoms of subacute toxicity in rats were, anorexia, loss of body weight, occasional convulsions and slight hepatic damage.

Chronic Oral Toxicity In Dogs :—Chronic administration to dogs resulted in anorexia, loss of body weight, ataxia, tonic and clonic convulsions, fatty degeneration of the liver and jaundice. These effects were reversible if the drug was stopped promptly.

Certain hematological changes have been observed when 25 mg. or more per Kg. of isonicotinic acid hydrazide or its isopropyl derivative are given repeatedly[1]. The total hemoglobin and oxyhemoglobin concentration of blood goes down. At the same time the sulphemoglobin concentration of blood rises when marsilid was used. This may further lead to hypoplastic anemia associated with raised leucocytic and reticulocytic counts and a raised urinary urobilinogen value. The liver is pale and bile dark. Hydrazines of isonicotinic acid do not have the depressive action on erythropoiesis as do phenylhydrazine or acetylphenylhydrazine.

In the chronic toxicity studies in dogs[1], the isopropyl derivative appears somewhat less toxic than the isonicotinic acid hydrazide in so far as the weight gain and general observations were concerned. On the basis of gross pathological changes in the tissues the reverse situations appear to exist. The hemorrhagic bone marrow noted in dogs receiving isopropyl derivative was not noted in dogs receiving comparable doses of isonicotinic acid hydrazide. The question of reversibility of these changes is being studied.

TOXICITY ENCOUNTERED DURING THE CHEMOTHERAPY OF HUMAN TUBERCULOSIS[15]

Five cases of advanced permanent tuberculosis were given subcutaneous injections of the glucosyl derivative of isonicotinic acid hydrazide in a dosage of 1 mg./Kg. body weight for the first three weeks and 2 mg./Kg. body weight for the second three weeks and 2 mg./Kg. body weight for the next three weeks.

Similar experiments were carried out in other patients using the isopropyl derivative and the original compound, isonicotinic acid hydrazide. The toxic reactions have been entirely of the " acute " variety. The symptomatology was largely related to the autonomic nervous system and consisted of sympathetic stimulation. Some patients complained of constipation, bladder sphincter disturbance and dryness of the mouth. Vertigo and transitory fall in blood-pressure and increasing pulse rate were also noticed in some cases. The central nervous system was also stimulated as shown by hyperactive reflexes, involuntary twitchings, insomnia and drowsiness. It is thus seen that the symptoms are essentially of a moderately acute variety[15]. No cases of parenchymatous toxicity have been encountered when therapeutic doses were used.

The lack of general pharmaco-dynamic properties of the hydrazides in dosages which have ameliorative effects in tuberculosis suggests that these agents would be free of side effects[1]. Selikoff[15] thus thought that constipation and retention of urine were of autonomic origin—due either to parasympathetic blocking or sympathetic stimulating properties. However, with the exception of a marked bronchiolytic effect exerted by the isopropyl compound against cholinergically induced bronchospasm in the guinea pig, little evidence is available for a parasympathetic blocking activity.

Dizziness, over alertness and insomnia are suggestive of a central nervous system stimulation[1].

Elmendorf and his colleagues[5] found no evidence of potentially serious toxic effects. On a dosage of 3 mg./Kg. per day, there was no indication of toxicity to the hemopoietic system and renal and hepatic function was not disturbed.

CLINICAL TRIAL IN HUMAN PULMONARY TUBERCULOSIS[13]

The first report on the clinical trial on isoniazid and its derivatives in human tuberculosis has come from Robitzek, Selikoff, and Ornstein[13]

Group No.	No. of patients.	Drug.	Dosage and date of starting.
1	17	Marsilid	2 mg./Kg./day divided into 3 doses from October 2.
			4 mg./Kg. from Nov. 20, 1951.
2	7	,,	2 mg./Kg. started on Oct. 15.
			4 mg./Kg. from Nov. 20.
3	7	,,	2 mg./Kg. from Oct. 25.
			4 mg./Kg. from Nov. 20.
4	29	,,	4 mg./Kg. Nov. 15.
5	17	,,	4 mg./Kg. Nov. 23.
6	10	,,	10 mg./Kg. Dec. 5.
7	11	Rimifon	2 mg./Kg. from Dec. 17, for one week, and afterwards:
	98		4 mg./Kg.

They have tried the drug in pulmonary tuberculosis in 92 patients, 54 males and 34 females, the majority of them being in the age groups 20 to 60 years and distributed as follows :

Of these, six cases were omitted for causes other than pulmonary tuberculosis.

Their basic criterion in the selection of cases has been very rigorous. No patient was selected in whom alternative therapy could reasonably be expected to provide clinical arrest. All patients suffered from extensive, bilateral, far advanced, active, progressive, caseous-pneumonic tuberculosis and in the pre-therapy period had failed to show improvement. None was found to be a suitable candidate for chemotherapeutic or antibiotic therapy, pneumothorax or pneumoperitoneum therapy, or any of the various surgical procedures. In almost all instances one or more of these procedures had been previously utilised. In short, only those patients found to be " hopeless " were accepted for therapy since there was no certainty that the drugs under investigation would exert significant chemotherapeutic effects and it was essential that no patient would be deprived of the benefits that might conceivably be anticipated from presently accepted valid methods of treatment. All patients had persistently positive sputum and had open cavities on roentgenograms. All were below normal weight, often very much below normal weight. Almost half were febrile and toxic. All showed either stationary or progressive disease on serial roentgenogram. Eleven per cent suffered from simultaneous tuberculous laryngitis ; many suffered from other forms of extra pulmonary tuberculous or non-pulmonary diseases (including tuberculous otitis, empyema, fistula in ano, tuberculous glossitis, amyloidosis and syphilis. The clinical trials were started after thorough laboratory investigations.

The seven month experience of these authors from June 1951 to January 1952 indicates that isonicotinic acid hydrazide and its derivatives, so far investigated, exert a profound and important therapeutic effect in human tuberculosis. To quote the authors' words, " the mortally ill patients we have studied have obtained therapeutic benefit beyond anything we have ever seen with any of the chemotherapeutic or antibiotic agents, previously utilised by us. Since our observations have been of limited duration, we cannot make any definitive statements as to the place this group of agents will ultimately assume. That this effect is profound, however, can be stated categorically".

CLINICAL RESULTS[13]

Effect on Temperature :—In every instance, the patients became afebrile within the first two weeks. Usually, the temperatures came down to normal within the first week. This consistent and dramatic effec- on fever occurred regardless of whether the fever was short or of long duration. It was found in every type of anatomical pulmonary lesion whether predominantly exudative, caseous-pneumonic or productive or massive combinations of all three varieties. This temperature drop was noted with all dosage ranges but apparently was more precipitous and more rapid in the higher dosage levels.

Toxicity :—Coincident with the fall in temperature and even otherwise in afebrile cases there was a rapid and profound reversal of apathy, asthenia, hypotonia, weakness, easy fatigue and exertional dyspnea. Toxicity was alleviated promptly after the institution of therapy and was noticeable within 48 hours in some cases. In every case, toxicity completely disappeared by the end of the second week. The restoration of normal skin turgor has been the first sign of decreased toxicity. The normal oiliness replaces the previously dry and flaky appearance. A feeling of well being often precedes the evident reduction in toxicity. In afebrile cases, the disappearance of toxicity often precedes the regaining of appetite and loss of fever.

Appetite :—Appetite has been improved in every patient in this study. Above the dosage level of 4 mg./Kg. of marsilid the resumption of appetite was invariable. The appetite became so ravenous that the consumption of food in these cases increased by 50 per cent.

Weight :—Although the gain in weight by no means represents the actual status of the lung condition, it is frequently indicative of the systemic effect of the tuberculous process on the metabolic state of the patient. Thus a gain in weight is a valuable guide to the therapeutic effectiveness of any anti-tuberculous compound. In the present series, the weight gained by patients was probably the maximum to be expected from the metabolic limitations of the human organism. Some patients have put on 3 to 5 pounds every week. Some others have put on 4 lb. in one week. In some cases, over 50 lb. have been gained within a period of 9 to 12 weeks. Almost all patients regained their normal weight within 4 to 16 weeks. The overall weight gained was approximately 2 lb. per patient per week. The effect is remarkable in that one is amazed to find the rapidity with which the human metabolic mechanism can re-establish itself once the toxicity of the disease process has been eliminated. In all cases the rapid weight gain was associated with enormous clinical improvement. The authors have shown that the weight gained was not due to water retention.

In the chronic feeding experiments in rats, evidence for a " growth stimulant action " was not observed. This is of interest because it indicates that the weight gain achieved by tuberculous patients receiving isoniazid is related to an increase in appetite secondary to reduction in the toxicity of the tissues rather than to a direct stimulation of the appetite by these compounds. It also tends to indicate that the weight gained in patients is not related to tissue inhibition to fluids by these drugs[1].

The rapid gain in weight in patients with relative pulmonary insufficiency due to gross structural damage to the lungs has brought fresh problems in its wake. The increased activity associated with relief from toxicity plus the added weight has occasionally led to exertional dyspnea. This reminds us of the onset of congestive heart failure following the antibiotic control of subacute bacterial endocarditis.

Effect on Cough and Expectoration :—In every case, cough was improved or disappeared and expectoration considerably decreased or disappeared. This effect was maximum with higher dosage ranges. The effect on cough was most noteworthy by the second week. One of the early indications of the decrease in cough was the improvement in sleep, the patient being no longer disturbed by cough at night. The quantity of sputum also was dramatically reduced. This effect on cough and expectoration was remarkable since chest roentgenograms of patients whose cough and expectoration have been relieved still show open cavities.

On the basis of the inability of these compounds to suppress salivary secretion, Benson and his colleagues[1] are inclined to interpret the clinical effects of sputum reduction in the tuberculous patient as a real chemotherapeutic effect of the drug on the tuberculous lesion and not just an effect upon general bronchial secretion. The change in the character of sputum supports this view.

Residual cough and expectoration may persist in cases with multiple-open cavities and bronchiectasis. The probable reason is this that isonicotinic acid hydrazide has no bacteriological action apart from that on acid fast bacilli. This suggests the simultaneous use of streptomycin or penicillin, initially for a few days, to remove the secondary infection.

Bacteriological Examination of the Sputum :—Within 4 to 15 weeks of treatment, approximately 25 per cent of the patients had sputa which did not contain tubercle bacilli. Another 28 per cent showed only occasional positive sputum. The authors state " we have seen no other chemotherapeutic or antibiotic agent in which 25 per cent of the " desperate risk", far advanced, bilateral, extensive, caseous, penumonic tuberculosis cases will show negative sputum within the short period of trial of therapy we have observed to-date in this series. It should be noted too that in many of the instances in which negative sputum was obtained, the conversion of the sputum occurred rapidly, often within the second or third week of therapy. This has usually been coincident with or shortly after the decrease in cough and expectoration.

Roentgen Changes :—There has been a more or less marked reabsorption of the exudative processes and in a number of cases cavity closure or marked reduction in cavity size occurred. Often several cavities have become smaller in size simultaneously.

Extra Pulmonary Tuberculosis :—The early reports of clinical trials indicate that the drug has an important chemotherapeutic effect in extra-pulmonary tuberculosis. In tuberculous laryngitis, there is a rapid relief from laryngeal symptoms. Tuberculous otitis media has been treated with rapid and marked success ; encouraging benefits has been reported in cases of tuberculous meningitis not responding to streptomycin. Tuberculous gastro-enteritis has shown marked and rapid improvement with complete relief of clinical symptoms. Tuberculous ulcers of the tongue have healed spectacularly though streptomycin had been a failure.

Bosworth and his colleagues[3] have tried marsilid in three cases of spinal tuberculosis and two cases of hip-bone tuberculosis associated with sinuses or psoas abscesses. In all cases, the temperature rapidly decreased. The discharge from sinuses showed an absence of acid fast bacilli after treatment and clinically the patients improved rapidly. Several sinuses have healed and the reaction around all decreased. This discharge was also markedly decreased. As the trial is of a very short duration, it is too early to draw any conclusions.

DOSAGE RECOMMENDED

Oral dosage of isonicotinic acid hydrazide is 3 to 5 mg./Kg. This dosage should be exceeded only with caution and when adequate laboratory facilities are available to detect signs of toxicity. Children with tuberculous meningitis have been treated with from 5 to 7 mg./Kg. body weight daily for 4 weeks or longer without any apparent toxic effects.

PRECAUTIONS

Watch for signs of stimulation of the central nervous system and, if necessary, reduce the dose. Since excretion occurs chiefly through the kidneys, the drug should be given with caution whenever renal function impairment is known to exist.

CONCLUSIONS

It is too early to draw any conclusions from the above findings. Time often deals unkindly with early reports on new remedies specially in the field of tuberculosis. There is no question that the drug holds great promise. Long experience in the use of the drug is required to correctly evaluate its real position in the field of tuberculosis.

Indications are that PAS will have a largely subsidiary and insignificant role to play in future. The clinical trials with isonicotinic acid hydrazide have been too short to determine the role of streptomycin in tuberculosis. Simultaneous use is indicated by some authorities. Probably, streptomycin will be required to a much less extent—to initiate the treatment for a few days or to control secondary infection in advanced cases. However, people must still rest and get other treatment and people with unknown cases of tuberculosis must still be discovered to start treatment. Nor can this drug repair structural damage caused by the tubercle bacillus. In the words of Gordon Meade, there is no indication so far that these drugs will eliminate the need for careful medical supervision, bed rest, collapse therapy, surgery and other proven methods of treatment. The hope remains that this discovery will take us a further stage in the attack on tuberculosis.

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The "Why" of Baldness.

New clues to the possible causes of baldness have been discovered in medical research laboratories of the University of Pennsylvania.

According to observers who were doing basis research on the skin related to cancer, they stumbled, virtually by accident, upon a chain of developments which tend to indicate that oil secreted by the human skin—the semi-fluid substance known as sebum may exert a controlling effect upon natural hair growth and constitute a leading causative agent in bringing about eventual baldness.—Philadelphia Medicine, American Practitioner, 2: 1084, 1951.

False Modesty Delays Diagnosis of Cancer.

False modesty seems to be an important factor in the death each year of 70,000 cancer victims whose embarrassment about doctors' check-ups causes them to put off getting help while a cure might still be possible, says Collie Small in Redbook Magazine. Approximately 50 per cent of the cancer in women is in the primary and secondary sex organs, and single women with cancer of the breast or cervix appear to delay longer than other victims. Men, took delay too long. One man's fatal delay was traced to his refusal to go to a cancer clinic because "people will know what I have". Still others delay because of financial difficulties.—Their epitaphs might well read: "I would rather be dead than in debt."

Doctors themselves are sometimes at fault for encouraging false modesty by not insisting on breast-pelvic or rectal examinations as a regular and indispensable part of routine physical examinations.—American Practitioner, 2: 1046, 1951.

A rule-of thumb method is offered for calculating the safe period in a menstrual cycle. An accurate record for menses for six consecutive months is kept. From the longest cycle, 12 days are detected and from the shortest cycle 19 days are detected. The two figures thus obtained give the limits between which the woman is assumed to be fertile. Thus, a woman whose cycle varies between 24 and 32 days must reckon that she is likely to conceive between the fifth and the 20th days of the cycle, accounting from the last day of her menstrual period.—Quoted from Family Matters, Lancet, 1: 57-58, 1952.

Did you know that!!!

The Green Sputum occurs when there is:—

(1) Stagnation of purulent sputum with poor excretion of verdo-peroxidase set free by the breakdown of leucocytes—*e.g.*, bronchiectasis, lung abscess, inhalation pneumonia.

(2) Bacterial contamination of sputum with *Ps. pyocyanea* usually outside the body, but occasionally inside.

(3) Severe jaundice, especially with hepatobronchial fistulae.—John Roberstson, A., Green Sputum, Lancet, 1: 12-15, 1952.

PROTEIN DEFICIENCY IN SURGICAL PATIENTS

RECOGNITION AND MANAGEMENT

K. N. Udupa *

Various nutritional factors especially the effect of protein deficiency in surgical patients have been receiving considerable attention of various investigators in recent years,[5], [13]. Since in a country like India, where such a deficiency is commonly met with in the majority of her people, one should be throughly conversant with the manifestation of this condition, as well as with the management of these patients under the best circumstances available.

Such nutritional deficiencies are commonly seen in surgical patients who are chronically sick and are suffering from some type of chronic suppurative disorder such as osteomyelitis, empyema, or large discharging ulcers. But now-a-days, there is a tendency amongst the practising surgeons to operate as soon as they can and also to give the newer antibiotics like penicillin in large quantities, without giving much attention towards improving the general condition of these patients The result of such therapy is that the morbidity and in some cases even the mortality rate remains fairly high.

It is obvious that whenever there is any chronic suppurative condition in the body, one looses enormous quantities of protein and other materials every day. Unless they are properly replaced in the form of food and drinks the body is liable to develop all the manifestations of hypoproteinemia and other nutritional deficiencies. Therefore, before any serious surgical procedures or any other active therapeutic measures are undertaken, one must try to restore the general condition of those patients to the normal or nearly normal level. This will enable them to withstand the strain of surgical treatment and also to develop a natural power of tissue regeneration. Although all types of nutritional deficiencies can develop in such patients, in this paper, I am mainly concerned with the most important clinical condition called hypoproteinemia and will discuss in detail the various causes, manifestations, and also the treatment given to such patients.

SOME BASIC PRINCIPLES

Wound healing in surgery mainly consists of regeneration of three tissues, namely epithelium, fibrous tissue, and blood vessels. For such regeneration, although all the nutritional elements are required in abun-

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dance, according to Ravdin and Zintel[12] protein and vitamin C are the most essential requirements, since lack of both or either of the two tends to produce wound disruption. In a normal person these essentials are promptly supplied from the surrounding area and also from other body stores such as the liver, muscles, bone marrow, *etc.* However, in those debilitated and chronically ill patients whose body stores have already become depleted, the supply from outside sources is of paramount importance for an early recovery.

It is an established fact that the proteins which are ingested by mouth are absorbed into the portal circulation as amino acids. According to Wright[17], a portion of these amino acids thus absorbed passes through the liver into the general circulation from where they are taken up by the tissues. These tissues use them normally to make up for wear and tear which occurs during activity. They also use them for manufacturing specific products like enzymes, hormones, blood proteins, and other secretory products. The remaining portion of the amino acids which is left behind in the liver undergoes a process of deamination by which the nitrogeneous NH_3 radicle is removed for the formation of urea. The other nitrogenous residue after the separation of the NH_3 radicle, is converted into glycogen to be utilised as such in the muslces, *etc.*, for supplying calories to the body. Thus the protein can supply both amino acids and calories, whereas fats and carbohydrates can only supply calories.

Normally the intake of nitrogenous substances (proteins) in the food balances nitrogen loss in the excreta. The equilibrium between anabolism (formation) and catabolism (destruction) of proteins is termed nitrogen balance. A positive nitrogen balance or nitrogen retention indicates new tissue protein formation in the form of cellular protoplasm, plasma proteins *etc.*, which occurs usually during growth and after recovery from wasting diseases. Similarly, a negative balance with break down of tissue protein occurs during the inadequate intake of proteins during many infectious diseases and after operations.

As emphasised by Wright[17], one should note that the supply of protein, only is not sufficient to maintain body health. Sufficient calories are also required for supplying energy to the body, the minimum of which is about 2000 calories to a resting person. If sufficient carbohydrates and fats are supplied in the diet, protein is spared from the duty of supplying energy, and is used mostly to increase the protein content of the body. Therefore carbohydrates and fats are often known as protein sparers., In addition to this, a sufficient intake of water and salts, as discussed by Udupa[15], is also very essential for a patient's smooth recovery. Similarly the vitamin requirement of the body should also be kept in mind and one should try to supply as much as is required during the course of treatment. Above all, surgical patients need mostly vitamin C for proper healing, the vitamin B complex for the proper assimilation of ingested foods, and vitamin K for maintaining hemostasis.

These are some of the basic principles without the knowledge of which one cannot plan various therapeutic measures to be discussed later in this paper.

CAUSES OF PROTEIN DEPLETION

1. *Lack of Protein Intake* :—
    - (*a*) Inadequate diet :—Either due to poverty or because of a lack of appetite, *i.e.*, a diet containing proteins is not taken in sufficient quantity.
    - (*b*) Poor absorption :—Due to some diseases of the gastro-intestinal canal like dysentery, sprue, intestinal tuberculosis ulcertative colitis, carcinoma, *etc.*, the absorption from the gastro-intestinal canal is impeded.
2. *Excessive Loss of Proteins from the Body* :—
    - (*a*) Excessive loss of proteins through the discharge of pus from large wounds, empyema, osteomyelitis, *etc.*
    - (*b*) Burns where the protein loss is not only external, but also internal.
    - (*c*) Peritonitis, where the protein loss is mostly internal.
    - (*d*) Renal diseases with albuminuria, where the albumin is lost in the urine.
    - (*e*) Increased break down of proteins in the body like thyrotoxicosis, infective fevers, *etc.*
3. *Increased Protein Demands* :—Rapid growth, heavy muscular work, pregnancy, lactation, *etc.* which need a large quantity of proteins.
4. *Defective Utilisation* :—Liver diseases, where the absorbed proteins are not properly synthesised and utilised in the body.

These are some of the main causes of protein depletion in surgical patients and whenever one comes across such patients, one should suspect protein depletion.

MANIFESTATION OF PROTEIN DEPLETION

(1) *Increased Susceptibility to Shock* :—In hypoproteinemia it has been found by Hollander *et al.* that the total blood volume becomes much less and the interstitial fluid increases. In such patients, according to Ravelin *et al.*, if there is any further loss of blood or fluid from the vessels as found in hemorrhage and shock, the patient is liable to collapse at a comparatively much earlier stage than would patients with normal protein contents. Therefore, detection of hypoproteinemia and its correction in the preoperative period is very essential in surgical patients.

(2) *Lowered Resistance to Infection* :—According to Cannon[3], rats fed on very low protein diet did not produce as much antibodies as the normally fed ones and that the rats of the former group could not resist infections as effectively as the latter. Therefore, it is quite evident from the above experiments that persons with a low protein content are unable to resist infections properly, because of the poor antibody formation.

(3) *Impairment of Wound Healing* :—As already discussed earlier and as thoroughly discussed by Ravelin and Zintel[12], the fibroblast and capillary activities, which are the main functions in wound healing, become much less and incomplete in patients with low proteins, mostly because of the absence of sufficient raw materials *i.e.*, proteins. Wound disruption is very common in such patients.

(4) *Anemia and Impaired Hemoglobin Formation* :—Anemia is found coexisting in most of the nutritional deficiency conditions. But hypoproteinemia has special reasons for producing anemia since hemoglobin is mainly produced from specialized amino acids and iron. Therefore, unless the proteins, which are the main constituents, are supplied in sufficient quantities, hemoglobin will not be manufactured in sufficient quantity. Therefore, hypoproteinemia is one of the main causes of anemia in these patients.

(5) *Decrease in Plasma Volume and Plasma Proteins* :—According to Chassin[4], plasma volume and blood volume always become less in cases of hypoproteinemia. In such cases, in the beginning, there occurs only a decrease in the fluid portion of the plasma so that the plasma protein level is maintained at the normal level. In the latter stages both the plasma volume and plasma protein level becomes less. Hence in the early stage of hypoproteinemia, a simple laboratory estimation of plasma proteins is not very useful unless along with it the total plasma volume is also measured. After treatment with high protein diets, the improvement occurs conversely with the increase in the plasma volume first followed by a raise in the plasma protein content.

(6) *Increased Volume of Interstitial Fluid and Development of Edema* :—Maintenance of proper osmotic pressure of the plasma is one of the important functions of the body proteins. Normally, there is a constant interchange of fluid between the capillaries and the tissue spaces leading to the maintenance of a constant fluid level in the blood by the sucking action of plasma proteins. In hypoproteinemia more fluid goes out into the interstitial space than the amount of fluid which comes back into the blood. Therefore. there is every likelihood of getting edema all over the body including the wound site. As emphasised by Jones and Eaton[7], such edema becomes more pronounced in the wounds of the gastrointestinal canal due probably to laxity of the tissues. Here the edema of hypoproteinemia plus the edema of operation and also the edema of slight transient infection may be sufficient to obstruct

the otherwise perfect gastroenterostomy.

(7) *General Symptoms* :—In addition to all the above manifestations, these patients are also liable to get any other general symptoms such as weight loss, weakness, lassitude, mental depression, pallor, low pulse rate, low blood pressure, and a low metabolic rate.

DIAGNOSIS

A complete history of the patient should always be taken especially with regard to his body constitution, recent weight loss, his appetite and diet habits. Similarly, a detailed history of the illness should also be taken with special emphasis on fevers, discharge of pus, *etc.*, as enumerated in the list of causative factors. While doing a physical examination, care should be taken to find various manifestations of protein depletion such as edema, low blood pressure, anemia, and impairment of wound healing, which are some of the important clinical findings of this condition readily recognisable by any clinician.

As already discussed, the laboratory examination of the total serum protein level is not of very much value for detecting hypoproteinemia. However, it is generally presumed that although a normal serum protein level does not exclude the possibility of hypoproteinemia, a laboratory finding of subnormal serum protein level is a good evidence of hypoproteinemia. Normally, the total serum protein level varies from 6.5 Gm. per cent to 8.5 Gm. per cent if determined by the copper sulphate specific gravity method as described by Low[9]. We made use of this method extensively in normal and abnormal persons, and we are convinced that it is a very useful and easy method to make a rough estimation of the total serum protein level. However, for the purpose of treatment of this condition we did not find it very necessary to determine the albumin and globulin level, although determination of these would have been of great academic value.

A few patients of ours, who were suspected to be suffering from protein deficiency, did not show a low protein content of the serum, although they had most of the other signs and symptoms of hypoproteinemia. The explanation for such a variation is, that most of such patients do suffer from some type of dehydration with concomitant hemoconcentration ; because of this the plasma protein level appeared at its normal level in these patients. Further, the routine method of testing the total serum protein level as mentioned above, may have a significant range of error. In this regard some investigators[2] have suggested that in order to increase the value of such laboratory determinations, estimation of the total plasma volume should also be made so as to measure the total circulating proteins. For example, if the total serum protein is 8 Gm. per cent and if the total plasma volume is 2500 cc., the total circulating plasma protein will be $\frac{2500}{100}$x 8—200 Gm. Theoretically this suggestion is a very sound one. But accuracy in the available method of determination of plasma volume cannot be relied upon completely and it gives great variation from person to person and also from time to time in the same person[4]. Therefore, we have come to the conclusion that careful history taking and physical examination are of great value for diagnosing this condition. All the above mentioned laboratory examinations are only meant to supplement our clinical findings.

Once the diagnosis of hypoproteinemia is made, the patient is put on one of the suitable hypoproteinemic regimes to be discussed later along with other treatments. Throughout the course of this regime it is our practice to record weekly the total protein contents, body weight, hemoglobin percentage and red blood cell counts. In addition, the amount of discharge, improvement in the wound healing, and also improvement in the edema, if present, are also recorded periodically. By closely observing these facts one can follow the rate of improvement that takes place with a particular regime of oral or parenteral medication, in various aspects of the condition. Of course, during the course of these regimes, the main treatment for eradicating the diseases for which he comes to the hospital is also given.

TREATMENT AND RESULTS

General Principle :—According to the National Research Council of the U.S.A. and as quoted by Chassin[4], optimum dosage of proteins is 1 Gm. per kilogram of body weight as a maintenance dose or in other words about 70 Gm. for an adult person weighing 154 lbs. However, for a debilitated and sick person who loses quite a large amount of proteins, daily in the discharges, this dosage is not sufficient. In order to have rapid and smooth recovery at least 2 to 4 Gm. of protein per kilogram of body weight should be given so that there is not only a nitrogen balance, but also a nitrogen retention in the body. This will enable the body to synthesise new tissues with great rapidity. Here one should always keep in mind that the protein requirement of a fully grown healthy adult is much less than that of a debilitated weak patient, and, along with proteins, sufficient calories should also be given to check the proteins being utilised for energy purposes. As already discussed, a resting person needs at least 2000 calories per day or about 30 calories per kilogram of body weight[13] to meet his basic requirements. In order to face this, sufficient carbohydrates and fats should be given every day, so that they can do their protein sparing to the maximum extent.

Route of Administration :—

(1) Oral :—The oral method of feeding patients with the required amounts of proteins, calories, vitamins, *etc.*, is the best method for any type of patient with hypoproteinemia. As Ravdin[13] has emphasised, not only is the oral route easier, cheaper and safer, but the same weight

of protein absorbed from the gastrointestinal tract gives a slightly greater nitrogen retention when given intravenously. However, some debilitated patients may not like to take their food by mouth, because of lack of vitality and appetite. Therefore in such patients, the proposed diets should not only be prescribed, but one should also see that all the quantities that have been prescribed are ingested by the patient. However, in very weak and debilitated patients and those who cannot take food by mouth due to disease such as peritonitis, intestinal obstruction *etc.*, the intravenous method should be adopted.

For oral feeding, food materials such as egg, fish, meat, milk *etc.*, which are of animal origin, and also various pulses like moong, masur, wheat, soya been, *etc.* which are of vegetable origin but rich in proteins, should be given in sufficient quantity, to meet the demands of individual patients. As Ravdin and Gimbel[13] emphasise, since there are no reserves of essential amino-acids in the body, the amount of protein required to maintain nitrogen equilibrium increases as the concentration of essential amino acids in the protein decreases. In general, the proteins of animal origin are superior to the vegetable proteins, but still there are many vegetable proteins which are almost as satisfactory in value as animal proteins.

However, amongst all the materials available for oral feeding, dried skimmed milk,* is one of the best sources or protein. It contains 35 per cent of whole protein (casein and lactalbumin) of high biologic value. In this connection Varco[16] has suggested the following formula for the oral intake of concentrated proteins :

Varco's Formula :—Skimmed milk powder (3oz.), eggs (6), egg white (2), glucose or sugar (9oz.), and water (32 oz).

If no other fluid is added to this formula, according to Varco, this will supply about 120 Gm. of protein in 1500 cc. of fluid. If necessary, water can be added to this to dilute the formula according to the needs. There are two disadvantages in the formula, namely, nausea and diarrhea. However, nausea can be checked by adding some flavouring agents and diarrhea by opiates. By considering all these facts we prepared our own formula for feeding our hypoproteinemic patients keeping in view the diet habits of the patients and also the financial and other circumstances. In our patients this was found to give very satisfactory results within a short time. It consists of the following :—Skimmed milk powder (4oz.,) or milk (2 seers), eggs (2), meat (8oz.), sugar (8oz.) and water upto 3 pints in 24 hours.

In addition to this, the patients were also allowed to take the usual hospital diet consisting of rice and pulses at noon and wheat bread and vegetables in the evening. Our patients took meat with rice and skimmed milk with sugar. Where skimmed milk was not available, they were allowed to take 2 seers of milk or its preparations like curds, *etc.*, every day. Eggs were taken in the morning, half boiled. This formula should supply about 120 Gm. of protein and about 400 Gm. of carbohydrate with a value of about 1600 calories at the minimum. The results obtained by giving this diet is very remarkable and has been given in the Table 1, and Fig. 1. These observations have been made only on selected patients although such diets are commonly given to all the debilitated surgical patients. If such patients can wait for a few days before the operation, then these diets, along with supplementary vitamins, iron and liver extract, are given during the preoperative period till they reach the nearly normal level. If the operation is an emergency, as for empyema, or peritonitis, these diets are given only after the operation. In such patients the wound cavity heals rapidly by forming healthy granulation tissue. The discharge becomes less, and the body weight increases. In fact, one can notice an all round improvement in the general condition of the patient. If, however, due to debility or some other cause, the patient is unable to take these diets by mouth, then the other routes should be adopted.

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* As supplied by Unicef.

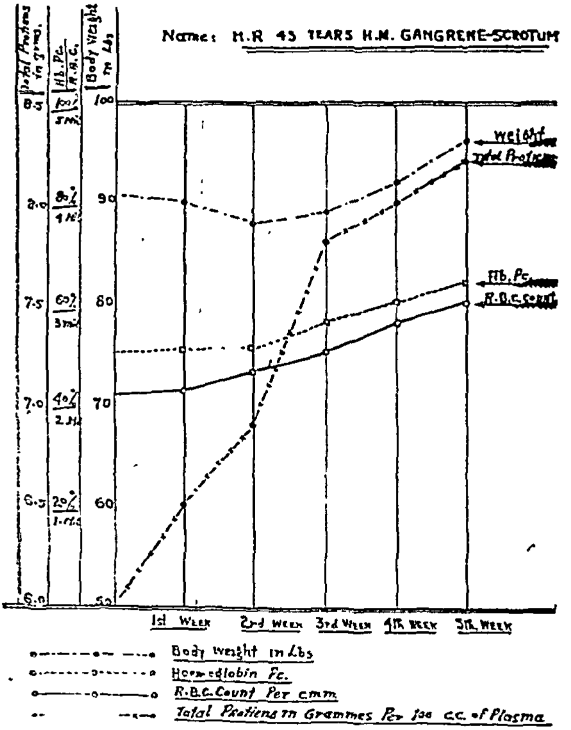

Fig. 1—shows the effect of high proteinic and high caloric diet given by oral route on various aspects of a hypoproteinemic surgical patient suffering from gangrene of the scrotum. In this, one will observe that increases in weight did not count in the first three weeks; because of loss of excessive edematous fluid from the body the plasma protein content improved during this period. Hemoglobin percentage and R.B.C. count gradually improved not only by the use of high protein diet, but also by the use of iron. There was striking improvement in the total protein content of the plasma by giving this diet, which rose from 6.0 Gm. at the time of admission to 8.25 Gm. at the time of discharge after 5 weeks. During this period, a large suppurative wound also healed rapidly and completely.

2. Tube feeding :—In this, the diet already mentioned for oral feeding, along with vitamin supplements, water and salts are given through an inlying gastric tube, such as the Ryle's tube[8], a gastrostomy or even jejunostomy tube as recently described by Mahadevan[10]. The

TABLE 1.—*Showing the Effect of High Proteinic and High Caloric Diet Given by Oral Route for Various Conditions in Hypoproteinemic Patients.*

S. No.	Name.	Age and Sex	Disease.	1st Week				2nd Week.				3rd Week.				4th Week.				5th Week.			
				R.B.C. in Mil.	Hb %	Wt. in lbs.	Total Pr. in Gm.	R.B.C. in Mil.	Hb %	Wt. in lbs.	Total Pr. in Gm.	R.B.C. in Mil.	Hb %	Wt. in lbs.	Total Pr. in G.m	R.B.C. in Mil.	Hb %	Wt. in lbs.	Total Pr. in Gm.	R.B.C. in Mil.	Hb %	Wt. in lbs.	Total Pr. in Gm.
1	HR	45M	Gangrene Scrotum	2.17	50	90	6.5	2.30	50	88	6.75	2.60	55	89	7.75	2.80	60	92	8.0	3.00	65	96	8.25
2	G	30M	Acute Empyema	2.00	50	90	6.75	2.40	50	88	7.4	2.40	50	88	7.4	2.70	55	90	7.5	..	..	..	..
3	S	40M	Acute Pyemic abscesses	2.35	50	98	6.70	2.50	55	101	7.3	2.90	60	104	7.6	..	..	..	..	..	..	..	..
4	B.R.	14M	ChronicOsteomyelitis Femur.	2.65	50	61	6.0	2.7	55	62	6.75	2.80	55	64	8.0	2.90	55	60	8.0	3.00	60	62	8.5
5	K	9F	Acute Peritonitis	2.17	50	30	6.0	2.4	50	32	6.75	2.5	55	33	7.0	..	..	..	..	..	..	..	..

diet articles should be properly ground and diluted in water. This should be given either by the continuous method or by the interrupted method. Diarrhea is the common complication of this method, probably due to contamination of the food and this should be avoided as far as possible by the judicious use of these diets. If this is also not possible, then the method of intravenous alimentation should be resorted to.

3. Intravenous alimentation :—During the past few years considerable progress has been made in methods of feeding patients by the parenteral route. The credit for the proper development of this science goes mainly to Elman[5] who by his extensive investigations brought this subject within the reach of every practising surgeon. According to him if the oral method is not practicable, the following amount of intravenous alimentation should be given, if there is not much abnormal loss of protein from the body. In the latter event the same quantity of amino acids should be added to the total quantity.

According to him 2000 cc. of 5 per cent protein hydrolysate in 5 per cent glucose and 100 cc. of 5 per cent glucose in 0.9 per cent saline will suffice for 24 hours. This will supply all the required amount of about 9 Gm. of salts, 3000 cc. of water, 100 Gm. of protein and about 150 Gm. of glucose. Although the amount of glucose that is supplied through this formula does not meet all the required amount of calories, still Elman[5] has proved by his investigations that by giving 150 Gm. of glucose, its protein sparing work is adequately maintained. Therefore, all the proteins given by this method will be utilised by the body as proteins only and not as calories. Recently, investigations carried out by Neptune *et al.*[11] showed that even fats can be given intravenously. If this method becomes well established, one can also give fat intravenously to meet the required amount of calories. Till then, Elman's method should be adopted universally since it is the best and the most practicable method. In this country, 5 per cent protein hydrolysate solution in 5 per cent glucose* serves the purpose very well, provided the preparation is a fresh one.

4. Plasma transfusion :—If the parenteral use of protein hydrolysate is not practicable, due to emergency, then plasma transfusion should be resorted to, for prompt recovery. Although the human plasma apparently seems to be the most logical material to replace serum proteins, in reality this is not so because most of the plasma proteins, when injected, leave the blood immediately to replace the deficient tissue proteins. Thus if a patient has a plasma protein level of 4 or 5 Gm. per cent and receives in all about 3000 cc. of plasma within the next 4 or 5 days, though this quantity is sufficient to replace the whole amount of plasma in the body, still the total serum protein level may not reach its

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* As prepared by the Bengal Immunity Co., Calcutta.

normal level. This is because, most of the proteins injected in the way of plasma, will go out into the tissue spaces and tissues. It has been reported by Chassin[4] that each gram of circulating protein of the blood is in equilibrium with 30 Gm. of tissue proteins. Therefore each 30 Gm. of injected plasma proteins will raise the circulating plasma protein of the body by one gram only, while the remaining 29 Gm. goes into the tissues to raise the tissue proteins. Hence it is but natural that only a fraction of the injected proteins goes actually to raise the level of the serum proteins.

According to Allen *et al*[1]. if the plasma is administered at the rate of 1000 cc. every day for about 12 to 13 days in chronically depleted patients, and at the rate of 500 cc. every day for 7 days in the acutely depleted patients, the plasma protein level comes to normal. They also observed that after a large and prolonged transfusion of plasma, the total plasma level increases temporarily but later on the excess of proteins goes into the tissues and the excess of fluid is excreted through the kidneys. Moreover, according to these observers, it takes about a week before a body can utilise these injected plasma proteins into tissue proteins.

Such a massive plasma transfusion to raise the protein content of the blood, is a very costly one, and in a country like India where availability of plasma for such a liberal use is also an important question, this method is hardly possible in a large number of patients. Moreover, by a massive plasma transfusion, one is also liable to get homogenous serum jaundice. Further, the plasma should not be given to edematous patients, since it contains more sodium chloride than necessary, which, incidentally, will increase the edema instead of decreasing it. Still, in cases of acute hypoproteinemia such as shock, burn, *etc.* the plasma transfusion is indispensable, and in fact is a life saving measure.

There is a difference of opinion amongst many investigators, as to whether in hypoproteinemic patients, protein hydrolysate or plasma should be administered. After doing certain practical observations in this field, I feel that if the plasma protein depletion is of an acute nature, as in burns or shock, the plasma transfusion should be given promptly. However, the availability of plasma in such a large quantity should also be a decisive factor for such therapy, if the hypoproteinemia is of chronic origin, and the patient cannot take the high proteinic diet by mouth due to a defective digestive system, then the protein hydrolysate should be given intravenously as suggested by Elman[5]. There is no special advantage for giving protein hydrolysate by the oral route, except in those whose digestive function is not in proper order, because the taste and smell of protein hydrolysate is usually not agreeable to patients. Therefore, if the digestive system is functioning normally and if the patient can wait for some time for the operation, a high protein and high caloric diet should be given by mouth. Parenteral feeding of protein hydrolysate should be resorted to only if other routes cannot be adopted.

SUMMARY

(1) Proper management of nutritional deficiencies, especially that of protein is one of the important items in the care of debilitated surgical patients.

(2) For wound healing a large amount of proteins and vitamin C are required at the local area. To achieve this, not only should protein and other factors be given in abundance, but also a large amount of calories, in the form of carbohydrates and fats, should be given for a proper utilisation of the proteins in the body.

(3) Amongst the various manifestations of protein depletion, impaired wound healing, anemia, edema—low blood pressure, increased susceptibility to shock, and a lowered resistance to infection, are some of the important ones. These, along with various causative factors, such as chronic discharge from the wounds *etc.* should lead one to think about protein depletion. Various laboratory tests, such as total plasma protein level estimation *etc.* are only supplementary to confirm the diagnosis.

(4) In the management, one should not only aim at nitrogen balance, but also nitrogen retention. Hence a diet roughly consisting of about 120 Gm. of protein with about 2000 calories consisting of carbohydrates and fats should be given for an adult weighing about 150 lb. Along with this, water, salts and vitamins should also be given in sufficient quantity.

(5) The oral route is the best method for the proper assimilation of proteins. Milk, skimmed milk powder, eggs, meat *etc.* are some of the important materials of animal origin which could be given orally to increase the protein content of the body. Soya beans, and certain pulses also, can supply sufficient proteins of vegetable origin if they are properly cooked and given in suitable form. However, animal proteins are much superior to vegetable proteins in this respect. If the oral route is not possible, then tube feeding through the inlying Ryle's tube or gastrostomy or jejunostomy tube should be resorted to.

(6) If the above routes are not possible, then intravenous alimentation as suggested by Elman should be tried. It consists of the intravenous administration of 2000 cc. of 5 per cent protein hydrolysate in 5 per cent glucose and 1000 cc. of 5 per cent glucose in normal saline in 24 hours. This roughly supplies all the requirements of protein, calories, salts and water to the body. If this regime is to be continued for a long time, then vitamins and other salts like calcium, iron *etc.* should also be given.

(7) In acute hypoproteinemia, due to shock, burns *etc.* a plasma transfusion, as discussed in the paper, is a life saving measure and should always be resorted to.

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New Method of Birth Control

A new method of birth control elaborated by S. N. Sanyal, of Calcutta, consists in administration of oil from *Pisum sativum* ("matar"). This oil is supposed to have an anti-vitamin-E action and its effect is quickly nullified by administering this vitamin. The animal results have been conclusive. The results in women are reported to be promising.

In rats administration of 1 cc. of this oil stopped conception for 6 to 8 weeks. The males and females were equally affected. At the onset of maturity the oil produced permanent sterility in rats. In clinical practice the oil is administered by injection. In women 1 cc. by mouth is given. The dose for men is not yet fixed. This method, according to its author is very cheap and does not hurt the religious feelings of the people. The author, it seems, got the inspiration about this method from the custom among the Hindus of taking *P. sativum* during the period of mourning.—Lancet, **1**: 57-58, 1952.

CURRENT MEDICAL LITERATURE

MEDICINE

SYMPTOMATIC RELIEF OF OSTEO-ARTHRITIS AND OSTEOPOROSIS WITH VITAMIN B_{12}, Hallahan, J. D.: Amer. Prac. 3: 27-32, 1952. 14 references, 1 table.

The author presents a preliminary report of the effect of vitamin B_{12} on 33 cases of osteo-arthritis and 2 cases of osteoporosis. All of the patients fulfilled the following criteria: (1) Clinical history of typical osteo-arthritis or osteoporosis. (2) Physical findings and/or roentgen ray evidence for questionable cases, both for osteoporosis and osteo-arthritis. (3) Discontinuation of other forms of therapy for at least one month before commencing vitamin B_{12} therapy. (4) Taking of no other antirheumatic or analgesic therapy while receiving vitamin B_{12}. Crystalline vitamin B_{12} in doses varying from 30 to 900 μg. intramuscularly were given per week for at least 3 successive weeks. All dosage schedules showed benefit but the optimum rapid results were obtained with 100 μg. per week. The following were the results in the osteo-arthritic group. Twenty patients benefitted with this treatment by the end of the first week and of these, 7 had obtained 100 per cent relief. By the end of the third week, 4 more showed partial relief and further two showed 100 per cent relief of symptoms. By the end of the third week, 30 of the 33 patients showed some benefit in this arbitrarily selected period. Both the two cases of osteoporosis were entirely asymptomatic by the third week. In those patients who had obtained only partial relief during the three-week period, it was found that continuation of the treatment brought about 100 per cent relief, the longest time taken for continued absence of symptoms being 5 months. The reason for the apparent effectiveness in the relief of symptoms of osteo-arthritis and osteoporosis is not known. No toxic effects were noted.

ERIC COELHO.

THE THIOURACIL DRUGS IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS, Herfort, and Livingstone, New York State J. of Med. 52: 431-436, 1952.

The thiouracil drugs have been employed on an empiric basis in patients with chronic ulcerative colitis. The authors report their experience in 15 patients. They were all ambulant and presented all the signs and symptoms of chronic ulcerative colitis with sigmoidoscopic and roentgenologic evidence. The diet was not regulated, each patient taking those foods that were tolerated by previous experience. Thiouracil was used in the treatment of the first eight patients and propyl-thiouracil in the remaining seven. Thiouracil dosage was 200 mg., three times daily. Propyl-thiouracil dosage was 100 mg. thrice daily. The treatment was continued for a minimum of 3 months and continued until significant improvement was noted.

Duration of treatment before manifest clinical improvement.—From one to four weeks maintenance of the drug were necessary before significant remission. This was evidenced in all cases by a decrease in the frequency of stools, abatement of abdominal cramps, disappearance of blood in the stools if originally present, and subsidence of fever when present.

Weight Gain.—Fourteen of the 15 patients gained weight, increases up to 43 per cent were observed.

B. M. R.—This was done in only 7 patients and in only one did the rate drop to minus 20 per cent. One patient developed a thyroid swelling.

Toxic Effects.—The only effects were arthralgia and periarticular swellings.

Proctoscopic Changes.—In seven patients the rectal mucosa returned to its normal appearance; in two, residual polypoid changes remained; in two, strictures already present prevent proctoscopy though they showed marked clinical improvement. Anal fistulas healed completely in two patients.

Relapses.—In two patients diarrhea returned to a significant degree in the course of the treatment and after an initially gratifying response. In both cases the recurrent diarrhea was transient.

The response in these 15 patients suggests that the thiouracil compounds may be of benefit in chronic ulcerative colitis. However, it must be pointed out that it is difficult to accurately assess the value of any therapeutic measure in these cases because the subjects of this disease are notoriously suggestible. Further trial is necessary. The authors cite experimental studies that suggest that thiouracil drugs act by increasing serum cholinesterase and so antagonise the effect of acetylcholine produced by vagal over-activity which is believed to be partly responsible for the disease.

E. J. BORGES.

THE USE OF ACTH IN THE TREATMENT OF ULCERATIVE COLITIS, Wirts, C. W., and Corrot, J. L.: Review of Gastroent, **19**: 13-18, 1952.

The authors have treated 10 patients with ulcerative colitis, all diagnosed in the routine manner and care being taken to exclude similar diseases. The dosage used has been 20 mg. to 40 mg. intramuscularly every 12 hours. The treatment was continued for 2 to 3 weeks with gradually reduced dose. In addition to ACTH all the patients were treated with the usual measures of bed rest, high protein diet, low in salt, with pot. chloride 2.0 to 6.0 Gm. per day, dicalcium phosphate 2.0 Gm. per day, testosterone propionate 25 mg. daily as a protein anabolic agent, vitamins, small transfusions when required.

From this study, ACTH appears to be a potent form of adjunct therapy in the treatment of ulcerative colitis. Remission of the colitis occurs up to 14 months but the underlying disease is apparently not cured.

J. B. Kirner in discussing this paper added his experience over a period of two years with 50 patients of ulcerative colitis. All these patients had not responded to a variety of therapeutic measures. In this study control observations were obtained with saline solution dispensed from ACTH-labelled bottles. ACTH, intravenously, has been of definite value in patients not responding to the standard method of administration; 20 mg. of ACTH have been administered in 500 cc. of 5 per cent glucose in distilled water, injected slowly over a period of eight hours. ACTH does not cure, but in conjunction with other established therapy the management of this disease has been somewhat easier, and an unfavourable trend may be reversed.

E. J. BORGES.

SURGERY

VARICOSE VEINS: SOME COMMENTS ON THE REPAIR OF SURGICAL FAILURES, Foote, R. R.: Postgraduate Med. J. **28**: 45-51, 1951. 5 references, 2 figs.

Varicose disease is a progressive condition showing steady deterioration over the years where surgical success is more noticeable when there is a marked incompetence of the valves of the superficial venous system associated with gross dilatation and tortuosity of the affected veins. The author has listed the failures in various groups though overlap may be present.

1. *Branches at the Sapheno-Femoral Junction Have Been Missed at the Time of the Original Operation.*—This is the most frequent finding and patients who suffer from this type of failure usually give the history that there is a period of definite benefit, recurrence as a rule appearing within 18 months.

2. *Cases Where the Internal Saphenous Has Not Been Ligated at all and the Internal Superficial Femoral Vein Has Been Ligated in Error.*—Both these two groups should be given the opportunity of surgical exploration and a further examination of the sapheno-femoral function. It is wise to make a larger incision and the branches may sometimes be defined by coughing. A sclerosant may also be used in addition.

3. *Those Cases in Which the External Saphenous Vein is Either Incompetent at the Time of the Original Operation or Has Become so Subsequently.*—This should have been noted at the first operation. It is worth trying sclerosant therapy in these cases as the fascia through which the vein passes may act as a valve.

4. *Cases in Which "Blow Outs" Develop After the First Operation or Have Not Been Attended to at the Time.*—In the lower leg these should be resected under local anesthesia. In the upper leg they should be treated by scarification of the intima.

5. *Cases which Develop Varices on the Inner Side of the Lower Leg after the Original Operation.*—Such cases as a rule require the 'ankle tie' operation and retrograde injection of a sclerosant through a plastic tube.

6. *Cases Who Have Been Operated on Correctly for Varicose Ulceration but Who Have Not Been Adequately Instructed Regarding the Subsequent Bandage Compression Treatment Which is Usually Necessary.*—The combination of surgery with local compression treatment is essential for healing of gravitational ulceration and the removal of the accompanying edema. If the elastic bandage is neglected the sticky 'elastoplast' type may have to be used.

7. *Cases Presenting Edematous Legs Shortly After Operation.*—Such patients are usually suffering from deep vein thrombosis either due to immobilization after the operation or to an over-all excess of sclerosant. Prevention is better than cure, but if the condition has developed it is essential to apply T. W. S. bandages correctly and to advise the patient to take plenty of exercise while these bandages are in place. Pressure should be maximum in the lower third of the limb and relaxed in the upward ascent so that they are comparatively loose just below the knee. Another possible cause of deep vein thrombosis is nipping of the femoral vein by the use of a clamp at the sapheno-femoral junction.

8. *Cases Which Have Been Operated Upon in the Presence of Deep Vein Thrombosis.*—Nothing much can be done in these cases except in the way of selected exercises with compression bandages and the avoidance wherever possible of all things which increase the gravitational factor.

9. *Persistence of Varicose Ulceration After Adequate Surgical Treatment, Due to the General Health of the Patient.*—Many of these patients will be found to be suffering from a severe anemia. Correction of this condition will in many cases cause healing. Tineal infection, too, can cause 'failure' to occur inspite of adequate surgical treatment.

10. *In-Adequate Follow-up*:—All patients should be seen at least every year after the operation as the condition is a progressive one and if adequate assessment of 'failure' is to be made.

EUSTACE J. DE SOUZA.

THE TECHNIQUE OF TRANSLUMBAR ARTERIOGRAPHY, Smith, P. G., Rush, T. W., and Evans, A. T.: J. A. M. A. 148: 255-258, 1952. 4 figures, 8 references.

The injection of radio-opaque fluid into the aorta and the subsequent visualisation of its branches, provides valuable information that is otherwise unobtainable by the present routinely utilised methods of urologic diagnosis. It is possible to differentiate between renal tumours and cysts. The potential function of a kidney whose ureter is obstructed, can be conclusively demonstrated when an intravenous pyelogram fails. The position of anomalous vessels not producing obstruction can be accurately determined as also multiple renal infarcts or even total occlusion of the renal artery. Extrarenal masses (retroperitoneal) can be readily differentiated from kidney masses. Recent technical developments have made for such simplicity and safety as to warrant its general use as a diagnostic instrument. On a basis of the results of a series of 668 aortic punctures, the authors believe that the selection of patients for arteriography is restricted only by uremia and the inability to tolerate thiopental sodium anesthesia. There have been no deaths and no extra aortic hemorrhage at operation following puncture; the morbidity has been limited to occasional diaphragmatic irritation, occasional minimal abdominal tenderness and most frequently, the complaint of pain and soreness at the skin puncture site. The authors have performed punctures on approximately 70 patients who were dying because of cancer, uremia or malignant hepertension. Autopsies were obtained in 36 cases. In only six was there blood outside the aorta at the puncture site and in none was the area larger than a golf ball. In the majority, the puncture site was not detectable.

Equipment consists of a 'sana-lok'10 cc. control syringe, male and female 'luer-lok' adapters, plastic tubing as used for intravenous sets, and 18 gauge, 6-inch needle with a stylet, and contrast medium.

The patient is prepared with a soap sud enema eight hours before the procedure and again two hours before. Nothing is taken by mouth for eight hours before arteriography. Morphine and atropine are given one hour before the procedure. The patient is placed prone on the X-ray table and a scout film is taken of the lower thorax, lumbar and sacral areas. The film is overexposed by 3 to 6 kv. more than is used for an ordinary intravenous pyelogram. The optimum exposure is 0.10 second. After the scout film, the patient is anesthetised. The needle is inserted about 8 cm. to the left of the spinous processes at the lower edge of the 12th rib passing ventrally, medially and superiorly, till it touches the body of the 12th thoracic vertebra when it is withdrawn and the direction slightly changed so as to advance more ventrally. This is done several times till the needle passes in step ladder form along the body till it slips past the left anterior edge of the vertebra. The stylet is removed and the needle advanced by 0.5 to 1 cm. until it enters the aorta. The syringe, tubing and adapters, filled with contrast medium are connected to the needle. Before injection is made, it is confirmed that there is a retrograde flow of blood into the tubing via the aorta and that there is pulsation of this column. The injection is now begun, 12 cc. being injected in 1½ to 2¼ seconds. As the last cubic centimeter is being injected, the first film is exposed to obtain the arteriogram. The needle is removed from the aorta as soon as the injection is completed. As rapidly as possible the cassette is changed and a second film is exposed to obtain a nephrogram.

EUSTACE J. DE SOUZA.

TRANSABDOMINAL CHOLANGIOGRAPHY, Carter, R. F., and Saypol, G. M.: J. A. M. A. 148: 253-255, 1952. 8 figures.

While the indirect means of diagnosis through liver function tests have played an important role, their greatest use in the future will probably be in determining the extent of liver damage and the proper medical therapy needed. The authors cite the evolution of the methods in use at the present time to portray the intrahepatic ducts At operation a dye was injected into the common hepatic duct to reveal stenosis. When atresia was found a longer needle was inserted through the stenotic area to find white bile above the stenosis. When this failed, a needle or trocar was passsed through the liver substance, aiming for the main right or left hepatic duct. Resistance was encountered on striking the duct. This resistance ceased as the point entered the lumen. As these intra-abdominal procedures were accompanied by no serious mishap, and encouraged by the fact that bleeding as well as bile drainage were slight as well as by the reports of the occasional obtaining of bile on needle biopsy, the authors decided to obtain a cholangiogram through the exploring needle. They selected a case which presented a picture of bile duct obstruction with such severe liver damage that primary abdominal exploration was contraindicated.

Under pentothal anesthesia, a No. 17 spinal needle without obturator was inserted through the abdominal wall into the left lobe of the liver in the direction of the bile ducts. When blood was obtained, the needle was slightly withdrawn or pushed a little further as the bile ducts are close to the hepatic vessels. After they obtained bile flowing from the needle, some was aspirated and 15 to 45 cc. of 35 per cent iodopyracet was injected. The needle was strapped to the skin for bile to continue to drain externally. Films were taken by the usual technique and a diagnosis of biliary obstruction at the porta hepatis was made. The patient improved and drained green and golden yellow bile through the retained needle which acted as an operative choledochostomy. Some days later, however, she had a massive hemorrhage (hematemesis and melena) and died. Autopsy revealed firm tumour nodules involving the upper portion of the common bile duct, the two hepatic bile ducts and the region of the neck of the gall-bladder.

EUSTACE J. DE SOUZA.

PEDIATRICS

MELENA IN THE NEWBORN INFANT, Rozenfeld, I. H., and McGrath, J. R.: Jour. of Ped. **40**: 180-181, 1952.

The authors treated a newborn infant who developed melena on the tenth day of life. The source of blood was traced to the mother's left nipple which was cracked and bleeding. The child made an uneventful recovery. Subsequently a study was made to determine the amount of ingested blood necessary to cause tarry stools in the newborn infant. Fresh blood was obtained by femoral puncture from a baby, heparinized and introduced into the same baby's stomach by means of a tube. Twenty-four children were observed. Of these, eight were given 2 cc. of blood, none had a tarry stool; one was given 2.6 cc. and had one tarry stool; seven were given 3 cc., four of these patients had tarry stools; the remaining eight children were each given 5 cc. and six of them had tarry stools. The infants who passed tarry stools did so from seven to seventeen hours after the blood was placed in the stomach. These results are interesting as they show that as little a quantity as 2.6 cc. of blood, when ingested, may cause a tarry stool in the newborn infant.

F. A. NAZARETH.

RESULTS OF ADMINISTRATION OF VITAMIN B_{12} TO NEWBORN INFANTS, Chinnock, R. F., and Rosenberg, H. W.: Journ. of Ped., **40**: 182-185.

As several reports had been published that vitamin B_{12} given orally was useful in promoting more rapid weight gain in young infants, in prematures, in malnourished children and, to a less extent, in well children, the authors report their results with vitamin B_{12} given orally. Full term infants were divided into three groups; one group was given vitamin B_{12} for 60 days, another group was given vitamin B_{12} for 30 days and the third group which acted as a control no vitamin B_{12} being given. The first two groups were given 5 mg. of the vitamin daily. A careful check was kept on the weight and height. All children were fed artificially. At the end of 60 days there was no appreciable difference between the three groups as regards weight and height, and the authors' results are at variance with other published reports.

F. A. NAZARETH.

DERMATOLOGY

USE OF THE HYPOSPRAY IN DERMATOLOGY, Preston, R. H., Goldman, L., and Thomson, R. G.: Arch. of Derm. and Syph. *62*: 327-339, 1951.

The authors investigated, both experimentally and clinically, the utility of a new apparatus for percutaneous injections wherein the usual hollow needle is dispensed with. It is called an hypospray or jet-injection apparatus. It is a metal apparatus (furnished by J. M. McKibbin, R. P. Scherer Corporation, Detroit) with spring-activated plungers. The pressure from these plungers forces out a sterile solution from a tiny orifice in a metal ampoule called a metapule. The solution thus ejected travels at great speed in the form of a fine spray. Penetration of the fluid into the skin will depend upon the amount of pressure, condition of the skin, angle of the instrument with the skin surface and the nature of the applicator tip at the orifice of the metapule. The instrument is calibrated for varying amounts of pressures and provides for the injection of 0.6 cc. to 1 cc. at a time. By the use of trypan blue and fluorescein the authors studied the course of the injected material into the skin both for penetration and lateral diffusion and for entry into the superficial veins. From this study it became apparent that for the hypospray to be of value in tropical dermatological therapy, a relatively greater proportion of the medication must be deposited in the superficial portion of the skin. For the achievement of this objective, various techniques had to be adopted. The text includes the photographs of (i) actual apparatus with different applicator tips, (ii) path of jet-spray in skin, (iii) tissue sections showing depth of jet-spray, and (iv) longitudinal section of the instrument showing the working of it.

Therapeutic studies have been carried out chiefly with regard to production of anesthesia in biopsy techniques and the therapy of circumscribed neuro-dermatitis, local inflammatory and parasitic disorders and other miscellaneous disorders including the use of sclerosing solutions for hemangiomas. The apparatus is a precision instrument and is an expensive one. One must be trained in its use. It produces a noise during its working which may be frightening the patients unfamiliar with this type of apparatus. The authors have particularly pointed out the relatively less pain produced by this method and hence its possible use in mass immunizations, pediatrics, insulin administration *etc.* There have been very few reactions to this technique. After 2 years of experience the authors feel that the hypospray will be a very useful addition in dermatotherapy if the jet-spray could be adjusted so that medication would be spread over a larger field within the dermis and even underneath.

T. K. MEHTA.

HERPES ZOSTER APPEARING AFTER TRAUMA, Klauder, J. V.: Arch of Derm. and Syph. **64**: 407-410, 1951. 2 figures. 4 references.

On review of literature, the author found that though there are frequent reports of herpes zoster occurring after peripheral nerve injury in European literature, there are but few such reports in English literature. This type of herpes zoster occurring in the wake of trauma to peripheral nerve is of importance from two view points:

(1) Laws governing workmen's compensation and (2) untoward effects of trauma and factors concerned in the awakening of viruses from a condition of dormancy.

The author had reported such cases in 1947 and now reports nine further cases in this article. The following interesting facts emerged from the study of these and other cases. Herpes zoster, with few exceptions, affected the nerve supplying the region injured. Injury to the skin or cornea was inflicted in various ways and was of variable degree, *e.g.* stroke of whip, foreign body in the cornea, twist and stretching during fall, bump and impact, burn, X-ray *etc.* There is an incubation period varying from one day to three weeks. Any interval beyond three weeks excludes trauma as the causal role in the production of herpes zoster. Herpes zoster has also occurred after intramuscular injections, lumbar puncture, osteopathic manipulation of the spine, and from deep roentgen therapy in the region of a ganglion.

Regarding the pathogenesis, the author propounds the following explanations: (1) that the virus of herpes zoster exists in body at the time of trauma, the latter producing a *locus minoris* resistance; (2) the virus is introduced at the time of injury, resulting in an ascending infection of the nerve, or (3) the nerve is involved through a transfer of dormant virus, by the blood stream, since the virus is neurotropic. Besides these exogenous factors, there are endogenous factors also, which awaken the dormant virus.

T. K. MEHTA.

GREEN NAILS, Moore M., and Marcus M. D.: Arch. of Derm. and Syph. 64: 499-505. 5 figures. 3 references.

Green nails are not a common occurrence. On review of the literature, the authors list the following as the etiological agents: (1) Green dyes, (2) Chemicals, (3) Infection with species of aspergillus, (4) Infection with some strains of *Candida albicans and C. tropicalis* and (5) secondary involvement with Ps. *aeruginosa* (*B. Pyocyaneus*). The first two are easy to diagnose from history *etc.* Among the onychomycosis, the aspergilli are perhaps the best known as producers of green nails. The various shades of green colours in aspergillus infection were attributed to the spores in the nail plate. There is caseous material underneath the free edge of the nail. Fungi can be demonstrated in this material. Occasionally other fungi like *C. albicans* and *C-tropicalis* also produce green nails, as proved by isolation of these fungi from two of the three cases reported by the authors. The green nails in the third case were probably due to secondary involvement with *B. pyocyaneus* though *C. tropicalis* was also isolated by culture. *B. pyocyaneus* is known to produce a bluish green pigment in culture media. It is called pyocyanin.

The text includes three case reports with photographs of affected nails and fungi and bacilli grown on Sabouruad's glucose agar media. Their microscopic and staining characters have been described: Case No. 1, that due to *C. tropicalis* and *B. pyocyaneus* was treated with mercury bichloride soaks (1: 1000, in 70% alcohol) twice daily and then with application of iodine crystals (2 %) in benzene. There was considerable improvement on this therapy.

T. K. MEHTA.

TREATMENT OF FOLLICULITIS KELOIDALIS CHRONICA NUCHEA (ACNE KELOID), Hollander, L.: Arch. of Derm. and Syph. 64: 639-640, 1951. 10 references.

After reviewing the historical evolution of this disease, the author lays down the following as the characteristic features of the disease, *viz.*, (1) very chronic and progressive disease, (2) it occurs almost exclusively in young men, round about 30 years of age, (3) the subjects have pink, curly, thick shafted hair. The author treated two patients with what he calls massive electrodesiccation on two separate occasions, at two-month intervals, plus diethylstillbesterol 10 mg. twice a day, for 8 months. No mastodynia developed following the latter therapy. After shaving and washing the affected area of the scalp and sterilizing it with alcohol, 2 per cent novocaine is injected locally to produce anesthesia. Then by the use of a unipolar electrodesiccating needle, as much of the keloidal structure as possible is destroyed. To avoid discomfort it is essential that the electrodesiccation be stopped for a cooling off period of two to three minutes at a time. All the charred tissue is removed with a pair of curved scissors taking care to avoid cutting into the undesiccated tissue. The electrodesiccation is completed when a trench of 1 to 1.5 cm. in depth is reached and when no palpable fibrous tissue is discerned. The wound is then dressed with 3 per cent aureomycin ointment every third day till healing is complete, which usually takes about three weeks. The procedure has to be repeated after about 2 months as some of the keloid regrows.

T. K. MEHTA.

EFFECTIVE APPLICATION OF BANTHINE IN DERMATOLOGY: Brown, C. S., and Sandler, I. L.: Arch. of Derm. and Syph. 64: 431-433, 1951. 4 references.

Banthine bromide is a new anticholinergic drug found effective in the treatment of hyperhidrosis and some other conditions associated with, or aggravated by, increased sweating. The dosage varied from 25 to 50 mg., 3 times a day, by mouth during first week, to 200 mg. per day, later on, until the desired clinical results were obtained. The duration of the disease was usually in terms of years. Both the groups of disorders responded well within a few weeks of starting the treatment and remained well during the observation period which varied from 6 weeks to 16 weeks. Results in 27 cases will be better appreciated from the following table.

Type of Disease.	Clinical Results.			
	No. of Patients.	Marked Improvement.	Moderate Improvement.	Slight Improvement.
Hyperhidrosis	5	5	0	0
Contact dermatitis	10	8	1	1
Intertrigo	6	3	2	1
Total	27	20	5	2
Results		74%	19%	7%

Seven patients complained of initial dryness of the mouth and three complained of blurring of vision as side effects of the drug. One patient noted temporary retention of urine. Besides the above indications, the authors feel that the drug is definitely useful in certain diseases of the sweat glands. According to them, the initial beneficial results obtained in such conditions as hydradenitis axillaris suppurativa, menopausal symptoms complicated with severe sweating, and nocturnal sweating, are sufficiently encouraging to warrant a more comprehensive clinical evaluation of the drug.

T. K. MEHTA.

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Examples. 1. Coller, F. A., and Maddock, W. G.; The Function of Peripheral Vasoconstriction, Ann. Surg. **100** : 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

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VAGINAL CYTOLOGY IN OVULATORY AND ANOVULATORY CYCLES *

P. N. Wahi † and Urmila Mehta ‡

In the management of sterility in the female, it is of fundamental importance to know whether one is dealing with a case of ovulatory failure or whether one has to look elsewhere for the cause of sterility. A number of methods have been devised to detect the occurrence of ovulation, but the most favourite single method has been the study of the uterine endometrium in the premenstrual period. Evidence of secretory activity at this stage is regarded as diagnostic of ovulation. Prior to the introduction of endometrial biopsy, this meant a dilatation and curettage under anesthesia. At the present time, the much simpler endometrial biopsy is being extensively employed. However, this method has still the disadvantage of being painful, requiring a special instrument and a trained individual to perform the operation.

The relation of vaginal cytology to the varying hormonal function of the ovary has been studied by many investigators.[1-16, 18, 19] Most workers agree upon the well defined response to estrogen activity in vaginal smears. Opinion, however, is not unanimous regarding a similar response to progesterone, and unless a change, diagnostic of luteal activity, is found in vaginal smears, this method cannot compete with endometrial biopsy in diagnosing ovulation. The present study was carried out in an attempt to elucidate this interesting problem.

The existence of two types of menstrual cycles in normally menstruating women is now well recognised. The first of these is the normal ovulatory cycle, in which the ripe follicle ruptures to expel the ovum and itself becomes converted into the corpus luteum. This body secretes

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* Paper read at the Annual Conference of the Associations of Pathologists of India, Hyderabad, in November 1951.

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both estrogen and progesterone as opposed to the follicle which elaborates only estrogen. A few days prior to the onset of menstrual bleeding the corpus luteum degenerates, eliciting a progesterone withdrawal bleeding from the endometrium. In the second type of cycle, designated as 'anovulatory,' the follicle having reached a particular stage of its development, begins to regress without having ruptured. Ovulation does not occur, no corpus luteum is formed and progesterone does not come into play. The menstrual flow of such cases is of the nature of an estrogen-withdrawal bleeding. At one time such cycles were believed to be rare, but more extensive study has shown them to be more frequent than once thought.

A valuable contribution to our knowledge of the vaginal smear was made by Rubenstein and Bendek.[16] According to them, the vaginal mucosa responds to rising estrogen levels by an increase in thickness. This process carries the most superficial layers away from their blood supply. Degenerative changes of the nature of cornification supervene, the cytoplasm loses its granularity and becomes hyaline and eosinophilic, and the nucleus becomes pyknotic. These scale-like cells are cast off in increasing numbers as estrogen activity increases. The degree of cornification of cells in the smear could therefore serve as an index of estrogen level. These workers believe that after ovulation, progesterone diminishes the cornifying effects of estrogen and produces a sloughing of cells which become curled up. On the basis of smear studies, they divided the normal menstrual cycle into a menstrual, postmenstrual, preovulatory, ovulatory, postovulatory and premenstrual phases.

The cells found in vaginal smears of normal women were classified by these workers[16] into eight types: type I cells—these are large squamous cells with prominent vesicular nuclei, a basophilic cytoplasm containing granules and a well defined cell outline. They are precornified cells and indicate low estrogen activity. Type II, III and IV cells represent the three stages in the process of cornification. The essential changes are a progressive hyalinization of the cytoplasm and pyknosis of the nucleus. The type IV cell is fully cornified, its nucleus may be fragmented and is indicative of maximum estrogen activity. Type V and VI cells are believed to indicate the presence of progesterone. The distinguishing feature of these cells is their curled and folded edge. The type VI cells are younger than those of type V. Type VII cells are fragmented. They indicate a withdrawal of both estrogenic and luteal hormones Type VIII cells are derived from deeper vaginal layers and appear in conditions characterized by low estrogenic activity and a thin vaginal mucosa. Such conditions prevail prior to puberty and at the time of the menopause. These cells are small and rounded and have large nuclei occupying half the cell area.

This classification of cells was employed during the present study. Besides the recognition of the type of vaginal cells found in the smears a detailed study of the erythrocytic, leucocytic, bacterial and mucus content of the smears was also made.

PURPOSE OF PRESENT STUDY

The purpose of the present study was to study the applicability of the vaginal smear examination to the diagnosis of the nature of sterility in women. A thorough study of serial vaginal smears taken during a number of ovulatory cycles was carried out and correlation attempted with serial endometrial biopsy findings during the same cycle. A careful search was particularly made during the second half of the cycle for some definite changes which could be attributed to progesterone activity. Similar correlative studies were carried out for anovulatory cycles. This was followed by a comparative study of the two types of menstrual cycles.

The fundamental difference between them lies in the absence of ovulation and progesterone activity in the anovulatory cycle. If therefore, a definite change attributable to progesterone activity could be found in the ovulatory cycle and if this change was not detected in the anovulatory cycle, this could be reasonably labelled as a specific response to progesterone. The presence of a feature fulfilling the above criteria could be looked upon as being diagnostic of ovulation.

MATERIAL AND METHODS

The material for this study was taken from 30 sterile women attending the gynecological outpatients department of the Sarojini Naidu Hospital, Agra. This group was selected for two reasons, first, the incidence of anovulatory cycles has been repeatedly shown to be higher in sterile women, and secondly, such patients are extremely co-operative to all measures directed towards the diagnosis and treatment of their symptoms.

General disease, inflammatory disease of the uterine adenexa and the presence of a pathological vaginal discharge were excluded by careful examination, before including the case in the series. This precaution was necessary on account of the fact that inflammatory lesions of the adenexa render endometrial biopsy a hazardous procedure. Further, the vaginal smear is profoundly altered by abnormal discharges and correct interpretation of the findings becomes difficult.

At the first visit to hospital a thorough personal and menstrual history was taken and in cases of secondary sterility an enquiry was made into the previous obstetric history also. A thorough vaginal examination was then made and the findings noted. The patient was asked to report for the first smear examination on the second day of the next menstrual period. This obviated the difficulty often encountered in determining the date of the last menstrual period in the hospital class of patients. During the course of study, douching, coitus, endocrine and intervaginal medication, conditions which are liable to affect the vaginal smear, were forbidden.

A vaginal smear was made on the second day of the menstrual period, and as far as possible on every other day till the onset of the next menstrual period. On each occasion two smears were made, the total number for each case was of course determined by the length of the cycle under consideration. In all about 900 smears were prepared and stained.

In cases having a normal 28-30 day cycle, an endometrial biopsy was performed on the 12th, 19th and 26th day of the cycle. If a secretory endometrium was obtained in either the first or the second specimen, the following biopsies were omitted. If, on the other hand, the 26th day specimen was reported 'proliferative,' the biopsy, if possible, was repeated within twelve hours of the onset of the next menstrual period. For shorter and longer cycles, the time of taking a biopsy was correspondingly altered.

The smear was prepared, fixed and stained according to Papanicalaou's technique already described.[20]

The endometrial biopsies were obtained by a small suction-type of biopsy curette. Since endometrial response to hormone stimulation might not be uniform, three pieces of tissue were obtained for sections on each occasion, one from each of the interior, posterior and lateral walls of the uterus. The tissue was fixed in formal saline. The sections were stained by hematoxylin and eosin technique. Special stains were used where necessary.

RESULTS

Ovulatory Cycles :—During the menstrual bleeding phase, a considerable exfoliation of the epithelial cells was observed. Fairly large groups of cells of types I, II, III and IV were seen in the smears. Clusters of endometrial cells, large number of leucocytes, erythrocytes and large strands of mucus completed the picture of the phase. (Fig. I).

The above picture gave place to one in which the epithelial cells in the smear were almost of the uncornified types I and II, and occurred in small groups (Fig. 2, 3). Erythrocytes were absent and leucocytes present in fair numbers along with variable amounts of mucus and bacteria.

From this postmenstrual stage showing smears with negligible cornification, a steady rise in the number of these cells was observed, indicating a rising estrogen activity. It was found that this process

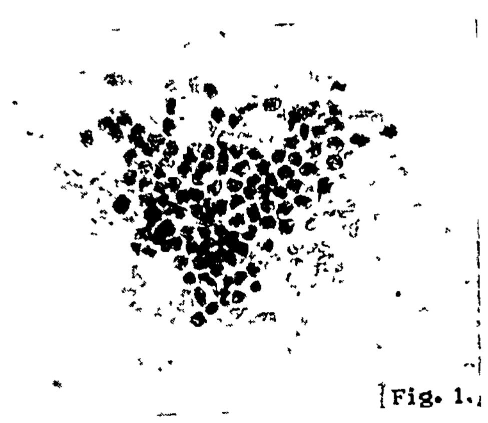

Fig. 1.—Third day smear of ovulatory cycle showing a cluster of endometrial cells with prominent nuclei and large numbers of erythrocytes. (X 430).

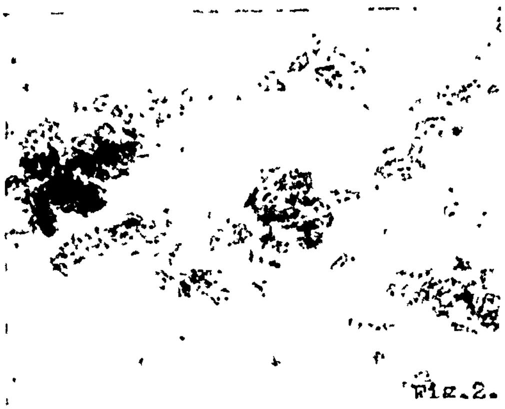

Fig. 2.—Seventh day smear of ovulatory cycle showing moderate cell grouping and preponderance of precornified cells of type I and II. (X 100).

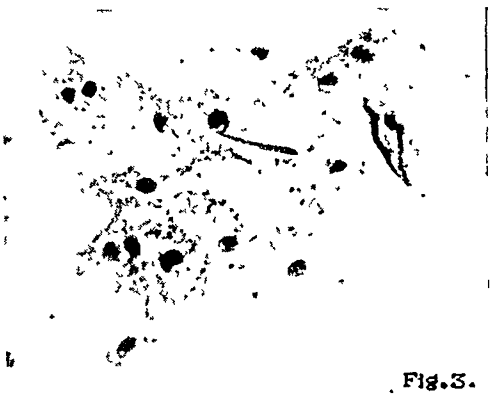

Fig. 3.—Seventh day smear of ovulatory cycle. Morphology of type I cells is clearly brought out. (X 430).

Fig. 4.—Smear of ovulatory cycle near the estrogen peak. Cell grouping is inconspicous, there is a preponderance of cornified cells and a 'clearing' of the smear is observed. (X 100).

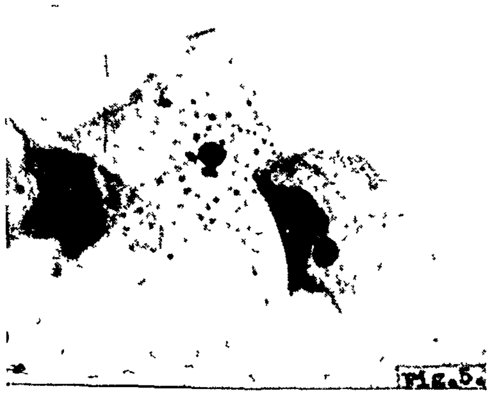

Fig. 5.—Showing a cell in the process of cornification with prominent cell granules (X 970).

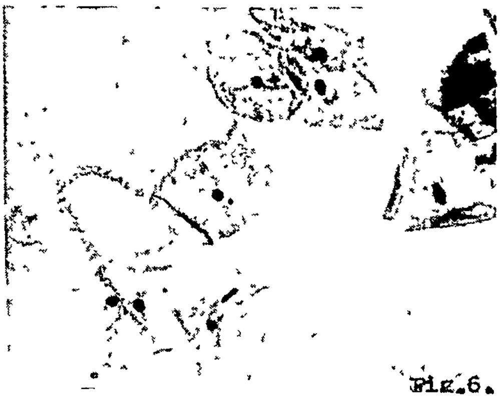

Fig. 6.—'Estrogen peak' smear of ovulatory cycle showing preponderance of type IV cells. (X 430).

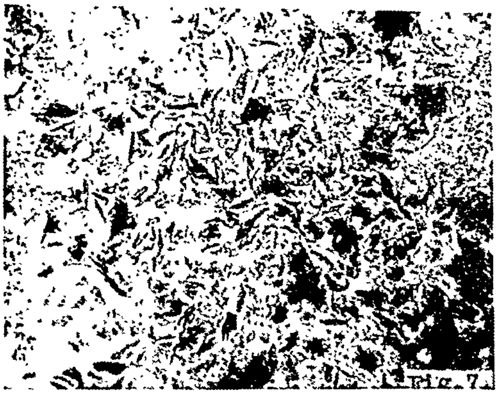

Fig. 7.—Smear following estrogen peak of ovulatory cycle. There is sudden increase in cell grouping with curling and folding of cell edges. (X 100).

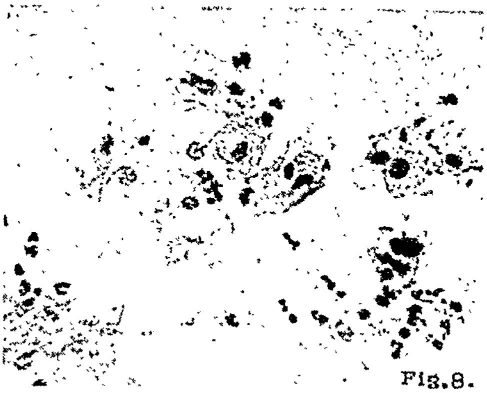

Fig. 8.—Premenstrual smear of ovulatory cycle (24th day) showing return of precornified cells of type I along with leucocytes. (X 430).

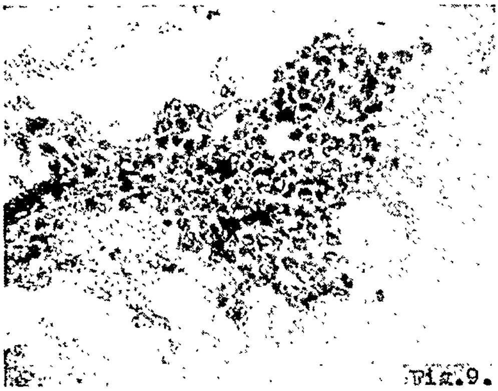

Fig. 9.—Third day smear of anovulatory cycle showing a cluster of endometrial cells. (X 430).

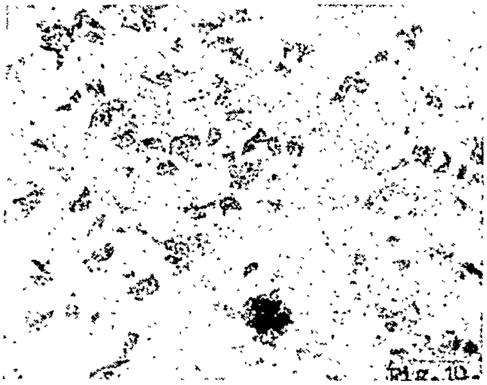

Fig. 10.—Seventh day smear of anovulatory cycle showing preponderance of type I cells with moderate grouping. (X 100).

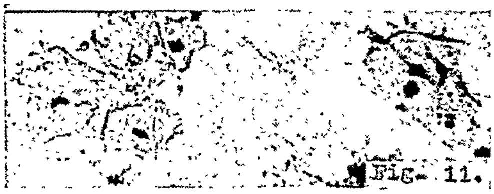

Fig. 11.—Seventh day smear of anovulatory cycle showing type I cells under greater magnification. (X 430).

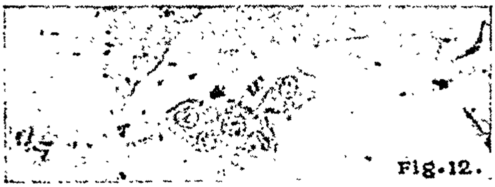

Fig. 12.—Smear of type I anovulatory cycle showing a group of deep vaginal cells of the outer basal type. (X 430).

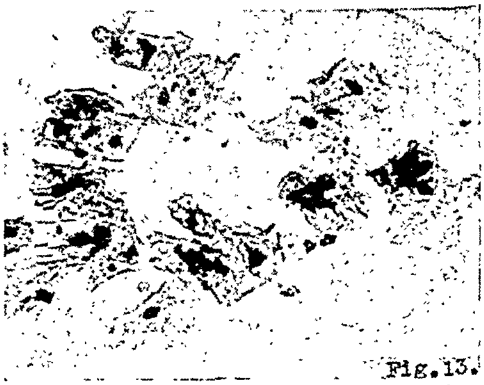

Fig. 13.—Premenstrual smear of type II anovulatory cycle showing persistence of cornified cells. (X 430).

followed a remarkably constant pattern in all the 12 ovulatory cycles. This is shown diagramatically in the following chart.

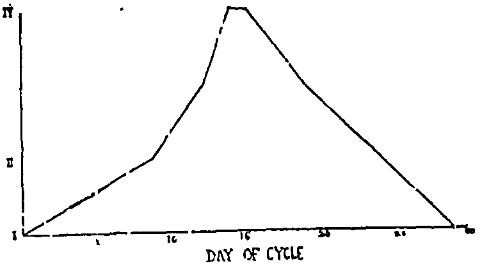

CHART 1.—Showing patterns of cornification of cells in an ovulatory cycle.

Simultaneously a remarkable clearing of the smear occurred. More and more isolated cells were seen and the amount of mucus and bacteria steadily diminished. (Figs. 4, 5). The culmination of these changes was the attainment of an estrogen peak in which smears showed cornified cells in large numbers. In the majority of cases this peak could be placed between the 10th and 17th day of cycle. (Fig. 7).

Following the above stage, a peculiar change was observed in smears of all these cases. Cells with markedly curled and folded edges and having a twisted appearance were observed in varying numbers. Along with the apperance of these cells, a considerable desquamation of epithelial cells was also seen in these smears which now looked strikingly different from those of the previous stage. (Fig. 7). This change was constantly seen following the peak of estrogen activity in 2 to 4 days.

The above phase was followed by one in which the proportion of cornified cells rapidly fell to postmenstrual levels, considerable cell grouping and exfoliations were maintained and bacteria, mucus and leucocytes reappeared. (Fig. 8). The curled and folded cells persisted to small numbers for variable periods of 4-8 days.

This picture merged into one in which the smear could be well described as 'dirty' owing to large amounts of bacteria, cell debris and fragmented cells of type VIII. Menstruation followed this stage.

Anovulatory Cycles :—During the menstrual phase evidence of exfoliation of the epithelial cells was constantly found. The degree of the process was variable. Generally speaking, the precornified cells (types I and II) were prominent. Cornified cells of type III were scarce. Red blood cells, leucocytes mucus and small clusters of endometrial cells (Fig. 9) were regularly seen.

The postmenstrual period was characterised by small irregular groups of type I and II cells with considerable numbers of leucocytes and bacteria, and an abundance of mucus. (Figs. 10 and 11).

From now onward the process of cornification followed three distinct trends, on the basis of which the anovulatory cycles were arbitrarily classified into type I, II and III.

In the type I cycles the number of cornified cells increased very slowly. Even at mid-cycle the precornified cells predominated in the smears. The leucocytes and bacterial content of the smear continued at more or less postmenstrual level and mucus persisted as a fairly heavy network. Following this stage, the number of cornified cells declined gradually so that premenstrual smear closely resembled the post-menstrual one. No curled and folded cells were seen. Another characteristic feature was the presence of type VIII cells—outer basal cells. (Fig. 12).

In the type II cycles, the proportion of cornified cells in the smears steadily increased to a peak level between the 10th and 20th days of the cycle. The cornified cells were mostly of type III. Mucus, bacteria and leucocytes were present in fair proportions. The regressive changes were very slow. The number of cornified cells declined very slowly so that even at commencement of the next menstrual bleeding, fairly large numbers of these cells were still present in the smear. Desquamation as evidenced by folding of edges and their getting crumpled together was not observed except in one case. However even in this case, the smears continued at their high level of cornification after the appearance of curled up cells. (Fig. 13).

In type III anovulatory cycles, the postmenstrual appearance rapidly altered to one with a large number of cornified cells of type III and IV. The peak was attained between the 10th to 17th day of the cycle. This was followed by regression depicted by a rapid fall in the number of cornified cells and a reappearance of bacteria, mucus and leucocytes. No curling of cells was seen.

Menstruation supervened on the regressive phase of each of the three types.

Changes observed in the anovulatory cycles as regards cell cornification and estrogen levels are represented diagramatically in chart 2. Each cell is taken into consideration on the day when its numbers reach the maximum in the smears. The remarkable similarity in the curves of the ovulatory cycle and type III anovulatory cycle is noteworthy.

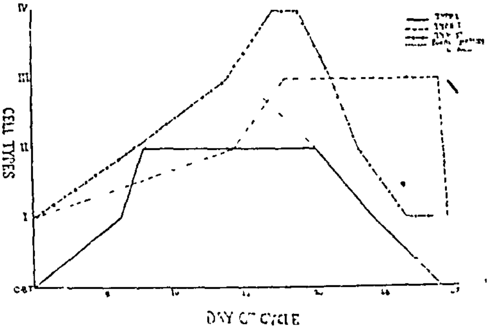

CHART 2.—Showing the types of cells seen on different days of the anovulatory menstrual cycle.

DISCUSSION

It appears from the observations that the anovulatory cycles differed from the ovulatory ones in the absence of desquamation and a decline in cornification after the estrogen peak. Evidence of desquamation was present in one case but in this case there was no decline in cornification.

Recently, Bonime[2] has reported the results of a study of vaginal smears in relation to the degree of ovarian development. He has studied smears of women at different ages and classified them into those of the infantile, prepubertal, pubertal, mature and menopausal ovarian ages. According to him, the sexual development can be regarded as normal only if the smears correspond to those which are normal for that chronological age. The pubertal smears described by him are characterised by follicle persistence and his description applies rather closely to the smears of the type II anovulatory cycle.

The type I anovulatory cycles stand in remarkable contrast with the ovulatory cycle. They are characterized by a monotonous appearance of the smears, poor cornification and a prevalence of leucocytes, mucus and bacteria throughout the cycle. The most noteworthy feature was the presence of deeper vaginal cells (outer basal cells) of type VIII in appreciable numbers throughout the cycle. These smears bear some resemblance to those of the prepubertal age group described by Bonime.[2]

A study of type I and II anovulatory cycles brings two interesting findings to light—first, that at least some of the sterile women having such cycles belong to a lower ovarian age than their chronological age and are hence not fully developed sexually. It is interesting to note that the outset of menstruation was delayed in six out of these ten cases. Secondly, the smears of these cycles differ from those of the ovulatory ones in the absence of desquamation and declining cornification following the estrogen peak.

The type III anovulatory cycles showed smears indistinguishable from those of the ovulatory ones as far as the pattern of cornification was concerned, but here again, the smears following the estrogen peak did not show any evidence of desquamation in three of these 4 cases. Decline of cornification was, however, evident in all of them. One of the above three cases, conceived in the cycle very next to the one during which she was investigated. It appears likely that such smears represent an occasional anovulatory cycle.

We find therefore, that the important difference between the smears of the ovulatory and anovulatory cycles was the desquamation and decline of cornification after the estrogen peak. This change in the smear picture acquires a great significance from the fact that it follows the estrogen peak closely, a time when ovulation could be presumed to occur. Ovulation brings about two important hormonal changes, firstly, a sudden drop in blood oestrogen and secondly the commencement of progesterone activity. The above two effects could be attributed either to a rapid estrogen withdrawal or to the appearance of progesterone.

That these changes are not due to estrogen withdrawal is borne out by the fact that they are absent from even the smears of type III anovulatory cycles which do show an estrogen withdrawal comparable to the ovulatory cycle. They could well be attributed to the action of progesterone but for the fact that in one case in this series, diagnosed as anovulatory by biopsy, they appeared immediately following the estrogen peak. It is to be noted however that regressive changes were unusually pronounced in the smears of this case. The smears showing the appearance of desquamation and declining cornification suddenly became 'dirty' with an abundance of fragmented cells, bacteria, mucus and leucocytes.

Are we, therefore, justified in regarding desquamation with declining cornification as an effect of progesterone ?

Some light may be thrown on this question by what Rubenstein[17] has mentioned about a group of cases of functional sterility. These patients appear to have a very brief luteal phase, during which satisfactory implantation of the fertilized ovum cannot occur. He based this conclusion on combined vaginal smear and basal body temperature studies. He found that the smears, after full development of the ovulatory picture, suddenly showed changes typical of the premenstrual phase indicating a rapid withdrawal of both estrogen and progesterone. The basal body temperature curve bore testimony to the accuracy of the smear findings by keeping at raised luteal levels for a very brief period. The endometrium of these cases was reported 'atrophic'·'secretory' during the premenstrual period.

The present study can only suggest that by a study of serial vaginal smears prepared during a complete cycle one can, in the majority of cases, distinguish the ovulatory from the anovulatory cycle. Whether the difference between them is a progesterone effect, it is not possible to say. This could only be proved if some day, cases of the type cited above are proved to be those of early luteal failure. Till then, the value of the vaginal smear method in the detection of ovulation must remain open to question.

CONCLUSIONS AND SUMMARY

Results of the study of serial vaginal smears and endometrial biopsies from 30 sterile women is presented and the applicability of the smear method in the diagnosis of ovulation is discussed.

The ovulatory menstrual cycle is characterised by a definite composite smear pattern built up by the successive phases—menstrual, postmenstrual, preovulatory, ovulatory, postovulatory and premenstrual phases. An isolated smear may yield no information.

The most important change is the desquamation or curling of cells and their grouping, accompanied by a decline in the numbers of cornified cells. This picture, following on the peak of estrogen activity when fully cornified cells predominate, may be regarded as diagnostic of ovulation. All the cases with such smear pattern showed evidence of ovulation in the biopsy specimens. It may, therefore, be reasonably concluded, that if the serial smears studied during a menstrual cycle show the above change, following this stage of maximum cornification, the occurrence of ovulation may be diagnosed to a considerable degree of certainty.

Smears varying widely from the above typical pattern are suggestive of ovulatory failure. The main variation is, either the degree of cornification remains very low throughout the cycle or if having come up to a fair level it is maintained till about the onset of the next menstrual period. Of the present series, 14 cases were found to have smears identical with this pattern and anovulatory menstruation was diagnosed by biopsy in all of them.

The diagnosis of the presence or absence or ovulation becomes difficult in smears which do not definitely approach either of the two patterns. In such cases a careful search should be made for desquamation and declining cornification in smears following the estrogen peak. If one or other is found singly, ovulation has probably not taken place. It may be that these represent an occasional anovulatory cycle as opposed to the habitually anovulatory cycles discussed above. Three such cases were encountered in the present study and one of these became pregnant in the next cycle.

No conclusion as to the etiology of the two important changes in the diagnosis of occurrence of ovulation, desquamation and coexistent declining cornification can be made from this study. They probably are the response to progesterone which brings about a sloughing of cells and counteracts the action of estrogen.

The vaginal smear method, therefore, offers a fairly accurate means of diagnosing the presence or absence of ovulation and perhaps possesses an additional advantage in that it gives an idea of the level of estrogen activity in the patient. It might also help in distinguishing an occasional anovulatory cycle from one which is the rule in a patient. However, the necessity for repeated examination by trained personnel, and the time required for such examination, would minimise its value in clinical practice.

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The doctor, armed with a new drug announced in *Time* (often in advance of the medical literature) must give it if he is to be financially successful—even though he may have intellectual doubts about its virtues. To be new, to be up-to-*Time*, is more important in most medical practice than to be a wise and human counsellor of sick humanity. The American Scene, Meiklejohn, A. P., Lancet, 1: 46, 1952.

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"..... Unfortunately the public tend to be more impressed by the luxury of the ambulance that brings them to hospital than by the clinical accuracy of the physicians or surgeons who treat them. More particularly is this so in retrospect, when, the illness fast improving, the attendant anxiety has abated. The tendency is, therefore, to spend more money on the material things such as ambulances—which can be readily appreciated by the uninformed laity—and less on the man who produces the diagnosis ....." Quoted from the Lancet, 2: 1205, 1951.

THE HORMONES OF THE ADRENAL MEDULLA

U. P. Basu *

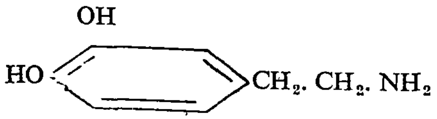
Adrenaline, the hormone of the mammalian adrenal medulla is one of the most useful drugs, we possess. Its isolation towards the earlier part of this century is now a matter of history ; but since its synthesis by Stolz and the pioneer experiments of Barger and Dale, extensive investigations have been carried out on the activities of natural sympathins.

FORMATION

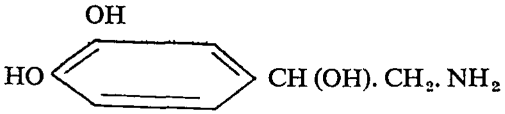
The genesis of these bodies is believed to be from the degradation products of proteinegenous amino acids of the diet and the tissues. It is known that tyrosine (I) under the influence of carboxylase may undergo decarboxylation to tyramine (II) and which in its turn may be oxidised to 3 : 4-dihydroxy phenylethylamine (III). If this amine suffers a β-oxidative change, a product becomes available which has now been isolated from the adrenal glands by Goldenberg *et al.*[4] but is known in the market under the name arterenol. This compound (IV) now termed nor-adrenaline, exists along with adrenaline (V) in some definite proportion in the adrenal medulla. The above formation of the hormones seems quite probable as Gurin and Delluva[5] have recently shown that in rats, phenylalanine (VI) labelled with C^{14} both in the carboxyl group and at the alpha carbon atom is converted to adrenaline in which the C^{14} is found at the terminal carbon atom (marked with asterisk) of the side chain of the adrenaline molecule (V).

(p) $HO.\ C_6H_4.\ CH_2.\ CH\ (COOH).\ NH_2$
(I)

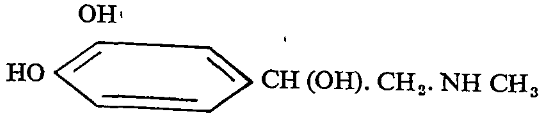
$HO.\ C_6H_4.\ CH_2.\ CH_2.\ NH_2$
(II)



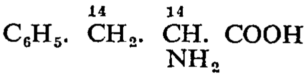
(III)



(IV)



(V)



$C_6H_5.\ \overset{14}{C}H_2.\ \underset{NH_2}{\overset{14}{C}H}.\ COOH$

(VI)

PHARMACOLOGY AND PHYSIOLOGY

The two hormones, adrenaline and nor-adrenaline, in the adrenal medulla, play an important role in the system whenever special demands are made on the body. Chemically, both are very susceptible and may undergo several bio-chemical changes. Their pharmacology is known to a considerable extent but little is yet known about their physiological functions. Adrenaline constricts the blood vessels (with the exception of the coronary vessels which are dilated), accelerates the heart and increases the pulse frequency ; inhibits peristalsis in the stomach, small intestine and large intestine ; dilates the bronchi ; stimulates salivary, gastric and biliary secretion, and exhibits glycogenolytic activity by promoting depolymerization of the storage carbohydrate, glycogen in the liver or muscles. The effect of adrenaline depends largely on the functional condition of the tissues. Its effect in an active muscle, is to dilate the blood vessels ; but when a muscle is at rest, it constricts the vessels. The pharmacodynamic activities of nor-adrenaline differ to some extent from adrenaline. Even its hyperglycemic action is much less marked than that of adrenaline (Goldenberg *et al.*[4]). It is, however, 50 per cent more potent than adrenaline in its pressor action and twice as active in its duration. It is of interest to note that in cases of powerful psychical excitement or strenuous physical activity, additional hormone is passed into the blood. The average weight of the adrenal glands, whether in man or woman, gradually increases from infancy to the age of 35-40 and then again slowly decreases. It is not, however, definitely known what happens to these hormones when they pass into the blood and suffer various chemical and biochemical changes.

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TRANSFORMATION

The nuclear dihydroxy groups, the secondary alcoholic group and the basic part in the side chain (IV and V) play a considerable role in the physiological action of the two hormones. Due to oxidative changes they give rise to a number of products ; these latter bodies by themselves, or, with the parent substances, may undergo a sort of condensation (Marquardt[8]) to afford a number of derivatives exerting pharmacological actions of diverse natures. Details are not yet available.

Adrenaline (or nor-adrenaline) may suffer deamination under the influence of a monoamine oxidase that is present in liver, to an aldehyde of the structure (VII) and the aldehyde thus formed might react with a second molecule of the hormone to form products of alkaloidal nature similar to papaverine (VIII). The latter compounds may exert an antispasmodic action on the vascular system. The opening up of the isoquinoline ring in (VIII) might afford a bis-γ-phenyl propyl ethyl amine (IX)-a type of compound which is again known to exert a stronger papaverine-like activity.

Both adrenaline and nor-adrenaline may also react with aldehydic bodies in the system to afford compounds (X) of the nature of cotarnine. It is known that cotarnine causes increased uterine contractions and is often used as a uterine hemostatic in certain hemorrhagic conditions.

Under favourable conditions the hormone may interact to form piperazine-like compounds (XI) whose pharmacological characteristics are also known.

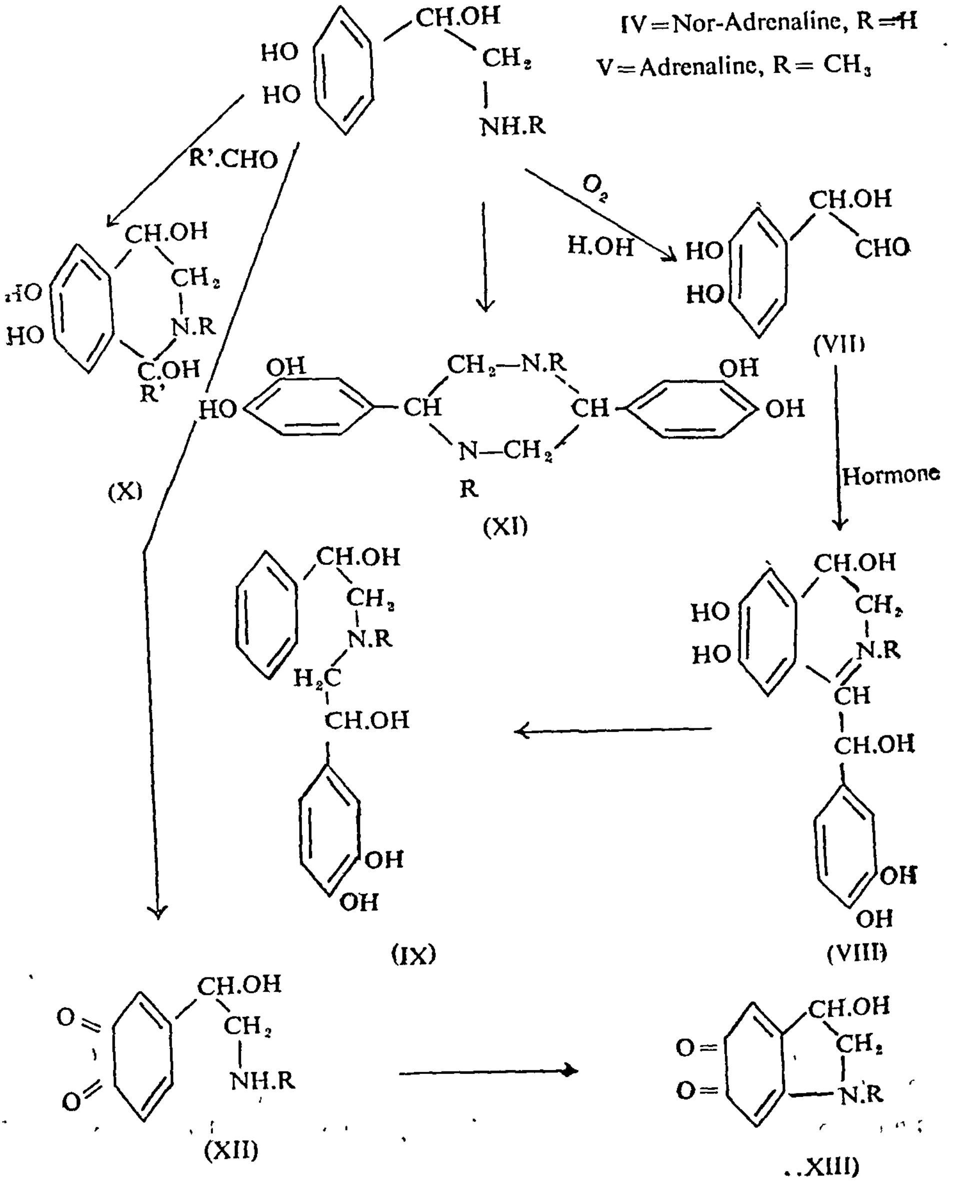
The influence of catechol oxidase (Aderhalden and Gugyenheim[1]) on adrenaline (also nor-adrenaline), or, on the conjugated sulfate ester of adrenaline as noticed by Richter[9], [10], converts the hormone to an indole (adrenochrome, XIII) through the quinone (XII). The adrenochrome is known to take part in a series of biological oxidations in the presence of co-enzyme I.

In such reactions the levo form of adrenaline may be more active. The difference in the behaviour of the sterioisomeric forms of these sympathomimetics is noticed in many other pharmacological actions. Thus, the levo adrenaline is about 20 times as active as the dextro isomer in the pressor action ; whereas the *dl*-compound possesses half the activity of the levo form. In maintaining the duration of the pressure the dextro variety, on the contrary, is three times and the *dl*-form twice as active as the levo one. Chemically also, the levo form of adrenaline is very unstable to air and light, whereas the dextro variety is comparatively stable. Various other pharmacological changes that might be brought about by altering the chemical structure of the adrenaline molecule have been reviewed in a previous article by Basu[3]. How a change in the optical rotation in an adrenaline hydrochloride solution is associated with the deterioration in its pressor action has been recently shown by Ganguly, Bose and Basu[6]. The following table shows that the above biological changes are not accompanied by any simultaneous chemical alteration.

TABLE 1.—*Change in Adrenaline Solution* (1 %) *on Storage.*

Period of Storage months.	Specific Rotation.	Potency.	
		Chemical.	Biological.
0	—50°	100.0	100
2	—34°	100.0	90
6	—25°	99.5	70
8	—11.5°	100.0	60
12	—6.0°	100.0	60

From the above it may be noticed that a number of physiologically active compounds might be obtained in the system for the bio-chemical transformations in and with the active principles of adrenal medulla. Besides, the physiological function of the hormones may also differ under other environmental conditions. The adrenal cortex which is now being so critically studied at present, is known to control the carbohydrate, protein, and mineral metabolism. Disturbed protein metabolism may affect the amount of sympathins in the medulla as they are possibly being formed from the protein breakdown products. Knowledge of the aftermath of drug therapy is gradually accumulating and we now find that one of the common drugs, salicylic acid, may lead to the production of cortisone-like steroids by activating the pituitary and suprarenal glands (Hetzel and Hines)[7]. The activity of the adrenal cortex is again known to be regulated by the corticotropic hormone of the anterior lobe of the pituitary called ACTH (adrenocorticotropic hormone). Stimulation of the suprarenal glands may then be the cause



IV = Nor-Adrenaline, R = H
V = Adrenaline, R = CH_3

for the alleviation of the disorder in rheumatic diseases. In this connection reference may be made to the recent observation of Brennecke *et al.*[2] on the effect of 8-amino quinolines in rheumatoid arthritis. The question arises as to what happens to the adrenaline molecule in the system during the changes cited above and after stimulation.

CONCLUSION

We are now becoming aware of the facts as to how the body uses adrenaline for various physiological needs. From the investigations that are being followed in different laboratories it is again becoming clear why a number of medicinal agents usually considered to be distinct and unrelated, might share a number of properties. The pharmacological characteristics of adrenaline and the possibility of its degradation and/or transformation to products of diverse nature, as shown in this review, tend to establish an inter-relation of properties of local anesthetics, cardiac stimulants, antispasmodics, analgesics, and diuretics. A detailed study of the pharmacology of compounds synthesised on the basis postulated above by a team of chemists, bio-chemists physiologists and clinicians, may yet open a new chapter in therapeutics.

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A CLINICAL STUDY OF A FEW CASES OF PARAPLEGIA*

G. V. Satyanarayanamurthi†

INTRODUCTION

This clinical study of cases of spastic paraplegia is presented with a view to emphasize the study of neurological cases by the general physician in the country. In view of the absence of neurological clinics in India, for the present it will devolve on the general physician for some time to come at least to deal with neurological cases as well as other special fields of medicine which in recent years have advanced both in methods of investigation and diagnosis to a very great extent. One day it may be possible to establish institutes and hospitals in this country entirely devoted to specialities like neurology but till such time it will be the duty of the general physician as best as possible to deal with these cases and give such relief as may be indicated.

INCIDENCE OF NEUROLOGICAL CASES

During the two year period from August 1949 to July 1951 the total number of admissions in my unit in the King George Hospital, Visakha-

TABLE 1.—*Incidence of Neurological Diseases.*

			Total	Percentage incidence.
Acute cerebral vascular accidents	Cerebral Hemorrhages	2	8	4.9
	Cerebral Thrombosis	6		
Meningitis	Tubercular	11	16	9.9
	Pneumococcal	3		
	H. Influenza	2		
Encephalitis			2	1.2
Cerebral Tumours			4	0.5
Aphasia			3	1.9
Epilepsy			20	12.3
Cerebellar Syndromes			5	6.2
Parkinsonism			5	6.2
Chorea			4	2.5
Mental deficiency			4	2.5
Cerebral syphilis			3	1.9
Ant. poliomyelitis			4	2.5
Hemiplegias			19	11.7
Paraplegias			29	17.9
Peripheral neuritis and peripheral nerve lesions			14	9.6
Myasthenia Gravis			2	1.2
Myopathies			2	1.2
Hysteria and other functional diseases			10	6.2
			162	100

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*Paper read at the Conference of the Association of Physicians of India, held at Hyderabad, in March, 1952.

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patnam (South India) was 2948. Out of these, 162 were patients suffering from diseases of the nervous system (5.5%). Table 1 gives a summary of the total percentage of incidence of various diseases of neurological nature. Out of these 162, 29 (17.9%) constitute paraplegias which is the subject of this paper :

Table 2 gives the total percentage of paraplegias under review grouped etiologically.

TABLE 2.—*Showing Total and Percentage Incidence of Paraplegias under Review Grouped Etiologically.*

			Total.	Percentage.
Compression of the cord :—				
(*a*) Vertebral causes syphilis	1	3	11	37.9
Compression fracture	1			
Exostosis due to fluorosis	1			
(*b*) Spinal tumours		4		
(*c*) Spinal compression of unknown etiology		4		
Syphilis of the cord			5	17.2
Toxic infective myelopathy			3	10.4
Spastic paraplegia with involvement of posterior columns			2	7
Chronic motor neurone diseases including (syphiltic amyotrophy 1)			2	7
Little's disease			1	3.5
Spastic paraplegia of unknown etiology			5	17.2
Total ..			29	100

PARAPLEGIAS DUE TO SPINAL TUMOURS PROVED AS SUCH POST-OPERATIVELY

Case 1. (S. No. 11) :—T. M., a Hindu male, aged 30 years, a labourer by occupation, was admitted on 15-3-50 for inability to use the lower limbs (9 months' duration). While carrying a loaded gunny bag he had sprained his back and thereafter noticed a gradually increasing weakness of the lower limbs. In the course of 4 months he was so disabled that he could walk about only with a stick. Three months subsequently he became bedridden. No other reliable information could be had regarding the progress of the disability. At the time of admission he had spastic paraplegia involving both lower limbs equally. There was lack of appreciation to pin prick and other modalities over the trunk and both lower limbs from below a horizontal line drawn over the nipples corresponding to the T4 T5 sensory dermatome level. There was defective relaxation of sphincters ; he was unable to initiate micturition or defecation. There was no tenderness or deformity of the spine.

Cerebrospinal fluid : 170 mm. pressure and jugular compression produced no appreciable change. The fluid was xanthochromic. Globulin+++. The Wassermann reaction of blood and cerebrospinal fluid was negative. A plain roentgenogram, of the spine showed a slight haziness of the body of the T2 and T4 vertebrae while screening on a tilt table after instilling 2 cc. of iodised oil into the subarachnoid indicated a block at the T3 T4 level.

Preoperative diagnosis : spinal compression by an extramedullary intradural tumour at the T3 T4 level.

A laminectomy on 13-5-50 over the T3 T4 T5 spinous processes showed that the cord was not pulsating ; on opening the theca a deep yellow fluid gushed out under pressure and a small globular swelling was noted to merge from the dorsal aspect of the cord on the left side indicating an extramedullary tumour 1/2" × 3/4" in size.

It was adherent to the cord by a broad pedicle which could not be easily separated and the tumour could not be delivered as a whole as the patient, at this stage, was deeply shocked and hence, as much as possible of the tumour was scooped out and sent for biopsy. Biopsy report showed it to be a neurofibroma.

Post-operatively, the patient made an uneventful recovery and on 1-8-50, nearly 2 1/2 months after operation, when a detailed neurological examination was made, it was found that he was able to walk by himself, unassisted, though he was not able to appreciate the ground as well as he should. He showed considerable recovery of sensations as a whole and had no difficulty about his micturition or defecation. Deep reflexes in the lower limbs were still exaggerated but not so grossly as prior to the operation. The Babinski reaction was still elicitable promptly. He was discharged on 2-8-50 for rehabilitation.

This patient turned up early this month (February 1952) stating that he had completely recovered subsequent to his discharge and was able to pursue his normal vocation for over an year. Unfortunately two months ago, after a stretch of walking for 10 miles he again suddenly relapsed into a state of mild paraplegia for which he now sought admission. He is under investigation.

Case 2. (S. No. 22) :—V. G., a Hindu female, aged 50 years, was admitted on 31-5-51 for inability to walk with shooting pain down the lower limbs and tingling and numbness (6 months). The present complaint started with pain starting first down the right leg, tingling and numbness of both lower limbs which gradually progressed to the present stage. She also complained of low back pain. There was weakness of both lower limbs with normal tone and no wasting. The gait was wide based. Reflexes : the plantar reflex was extensor on the right and not elicited on the left. Other jerks were not grossly altered. There was difficulty in initiating micturition. Sensory functions were not disturbed objectively.

Cerebrospinal fluid was not under increased pressure (40 mm.). Jugular compression however produced no change. It was xanthochromic, proteins, 1250 mg., globulin +++. The Wassermann reaction of the cerebrospinal fluid and blood was negative. A plain roentgenogram of the lumbar spine showed erosion of the pedicles of the 1st and 2nd lumbar vertebrae.

Preoperative diagnosis : Spinal compression due to spinal tumour localised to L1 L2.

A laminectomy over the lumbar vertebrae on 15-3-51 showed that the dura was markedly thickened and friable, and on opening it a cystic swelling of the size of a large pea presented itself to the right of the cord from its dorsal aspect. This was laid open and clear fluid exuded from the dura and the cyst wall was cleared. Biopsy revealed it to be a neurofibroma showing cystic and hyaline degeneration.

The patient was discharged on 8-5-51 ; she was relieved of her pains around the loin and legs and was able to walk about with a stick and was free from her bladder trouble.

Case 3. (S. No. 25) :—K. K., a Hindu female, aged 20 years , was admitted on 31-1-51 for inability to walk (3 months) ; the complaint began with pain radiating on the right side midway between the right costal margin and umbilicus. Later she noticed dullness of sensation of both legs and weakness of the right lower limb and gradually of the left lower limb also. The patient at the time of admission showed typical spastic paraplegia with occasional flexor spasms of the lower limbs more marked on the right side than on the left. There was lack of appreciation of sensation of all modalities over both lower limbs and the lower half of the abdomen below a horizontal line 2" above the umbilicus corresponding to the T8 spinal dermatome. There was precipitancy of micturition and defecation.

Cerebrospinal fluid showed xanthochromia and was under normal pressure but this pressure was not changed by jugular compression ; 250 mg. of proteins and globulin ++. The Wassermann reaction of blood and cerebrospinal fluid was negative. A plain roentgenogram of the dorsal spine was non-contributory while with lipiodol both by the cisternal and lumbar routes revealed a block at the level of the 7th and 8th vertebrae.

Preoperative diagnosis : spinal compression ; spinal tumour intradural and extramedullary localised to the 6th or 7th dorsal spine.

A laminectomy on 2-7-51 showed a tumour 3/4" × 1/2" about the 7th dorsal vertebra located to the right and ventral to the spinal cord ; biopsy showed it to be a neurofibroma.

The patient had a stormy post-operative period with meningitis which was controlled by appropriate treatment and on a review of the case a month after the operation it was found that the sensations definitely improved though they were not normal.

The patient was able to appreciate the fullness of the bladder and rectum though the precipitancy continued ; deep reflexes could not be elicited while there was hyperreflexia prior to operation. The motor power in the lower limbs showed no improvement but there was relief from the flexor spasms. She was discharged on 20-6-51 on request.

Case 4. (S. No. 28):—D. A., a Hindu male, was admitted on 27-1-51 for inability to walk with tingling and numbness and pain in the upper abdomen (8 months). The complaint started with tingling and numbness of the lower extremities and upper abdominal pain radiating from the back. Five months subsequently he could not walk without the help of a stick and a month later he became bedridden. He was stricken with flexor spasms during the month prior to admission and had developed a defect in initiating micturition and defecation for two months prior to admission. At the time of admission the patient was lying in bed with legs drawn up in a state of flexion, both lower limbs were weak and hypertonic with moderate wasting of both thighs and legs more on the left than on the right. Deep reflexes could not be elicited ; the plantar response was extensor on both sides. Anesthesia was present to all modalities of sensation from below the level of umbilicus corresponding to the T10 dermatome. There was still the defect in initiating micturition and defecation.

The cerebrospinal fluid was of a light yellow colour with normal pressure but jugular compression elicited no change and the protein content was 200 mg., globulin +. The Wassermann reaction of the cerebrospinal fluid and blood was negative. A plain roentgenogram of the spine was non-contributory while lipiodol through cisternal and spinal routes revealed a block between the 8th and 9th dorsal vertebrae. (Figs. 1 and 2).

Preoperative diagnosis : Spinal compression due to spinal tumour localised to the T8 and T9 dorsal spine.

A laminectomy of the 7, 8 and 9th dorsal vertebrae on 28-7-51 showed that the cord was dense and deviated to the right. On opening the dura a fairly large intradural extramedullary tumour was found dorsolateral to the cord on the left side about the level of the 8th dorsal spine pushing the cord to the right ; the tumour was irregular, of the size of an almond, and could be removed entire. Biopsy proved it to be a neurofibroma. The patient showed dramatic improvement following the operation. The root pains in the legs disappeared and he could move his legs a little. He could voluntarily evacuate the bladder and rectum. At the time of discharge in December 1951 he could walk about and was free from all symptoms.

Comment :—These four cases of intradural and extramedullary tumours of the spinal cord were diagnosed preoperatively and proved as such on the operation table. This is the commonest type of tumour, constituting, according to accepted statistics, as much as 67 per cent. They are easy of operative interference, nearly two third's of them being located on the dorsal aspect of the cord, but adhesions to the theca or cystic degeneration of the tumour may give rise to difficulties as evidenced in these cases.

As far as the usual type of hospital patient is concerned, in my part of the country it is very difficult to get a strictly chronological history which is a matter of great importance in all neurological cases. Very patient interrogation and repeated physical examination is necessary in these cases.

Though a general surgeon may, and can tackle these cases, a suitably trained neurosurgeon is the proper person to handle them. Post-operatively a long period of convalesence is inevitable and a general surgeon's wards are unsuitable for such. Even more essential is rehabilitation of the patient with suitable physiotherapy which is not yet in evidence in the medical institutions in this country.

DOUBTFUL SPINAL TUMOURS

Case 5. (Serial No. 12):—A male, 35 years of age, was admitted on 9-4-50 with a complaint of dribbling of urine (8 months), with difficulty in walking for 2 months. Physical examination showed spasticity of the lower limbs with exaggerated deep reflexes but no clonus, bilateral positive Babinski reaction, lack of appreciation of sensation to all modalities from the Tll to T12 segments in the lower limbs except joint sense which was present. There were occasional flexor spasms and incontinence of urine. Cerebrospinal fluid and blood showed no abnormality. A myelogram showed discontinuity between T12 and L4, but was inconclusive. Exploratory laminectomy was done and there was no evidence of any pathological lesion.

The patient died the day after the operation and autopsy showed and confirmed the negative clinical and operation findings. Serial sections also did not reveal any abnormal histology.

Case 6. (Serial No. 7) :—A male, aged 50 years, was admitted on 14-1-50 with dragging pains along the costal margins and inability to walk (one month). The stiffness of the left leg started first and the disability gradually spread to the right with shooting pains down the legs.

Physical examination revealed a left foot drop with weakness and wasting of the muscles. The knee jerk and ankle jerk were impaired on the left, though the Babinski reaction was elicited on both sides. Sensations to touch, pin prick and temperature were diminished from about the level of the umbilicus down both the lower limbs. There was tenderness along the spine at T8 and T10. The cerebrospinal fluid pressure was normal ; jugular compression elicited no rise in the C. S. F. pressure, globulin, + and proteins, 45 mg ; The Wassermann reaction of blood and cerebrospinal fluid was negative. A plain roentgenogram of the spine, and one with lipiodol showed no abnormality.

Exploratory laminectomy over D6 D7 and D8 revealed no lesion and there was no improvement following operative interference.

Case 7. (Serial No. 8) :—A female aged 65 years, was admitted on 25-1-50 with a complaint of inability to walk and tingling and numbness of 10 1/2 months' duration.

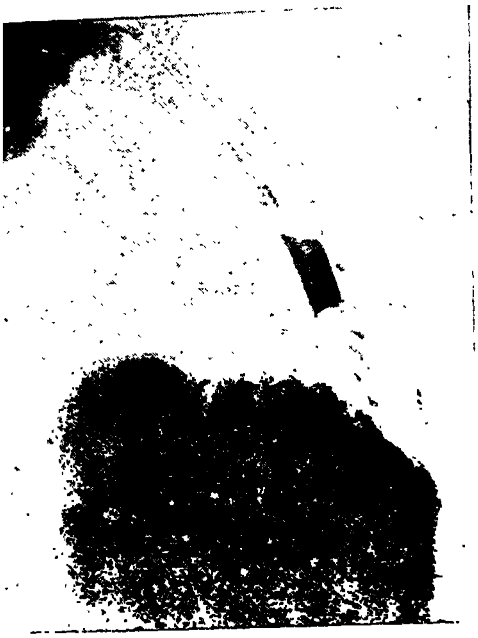

Fig. 1.—Case 4. Myelogram by cisternal route showing block at T8 T9. Lateral view.

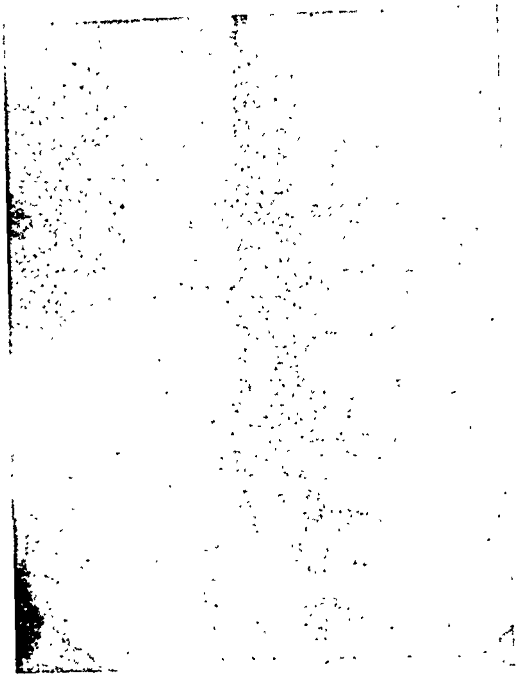

Fig. 2.—Same as Fig. 1, A. P. view.

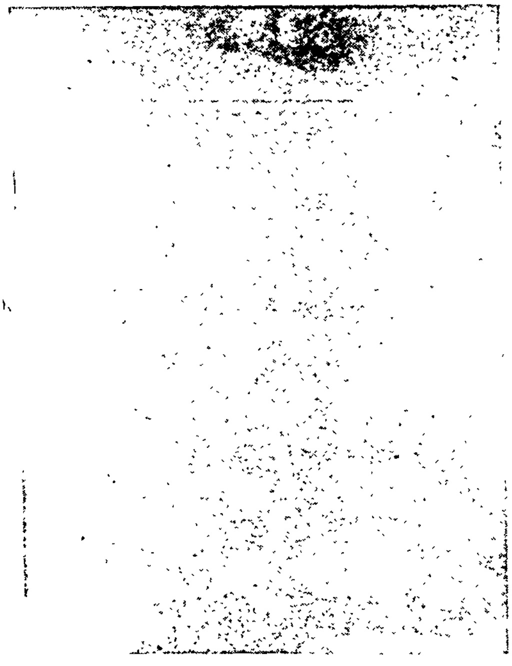

Fig. 3.—Case 9. X-ray of cervical Spine—A. P. view. Showing increased density of the body of the 6th cervical vertebra with new bone formation on either side of the 4th, 5th and 6th cervical vertebrae.

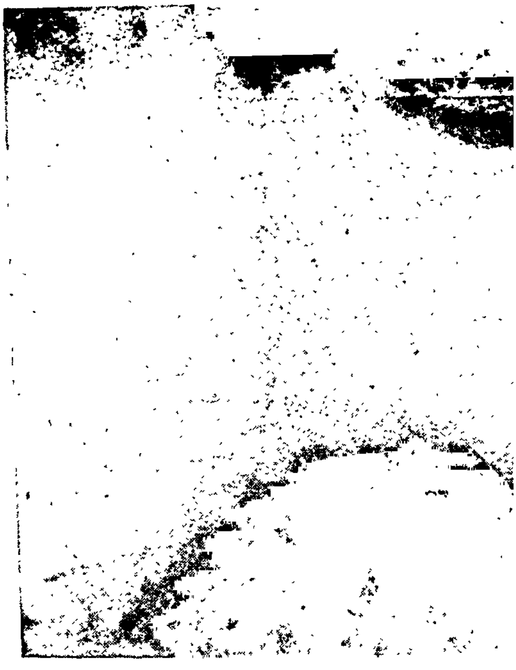

Fig. 4.—Case 9. Same as Fig. 3. Lateral view. Showing obliteration of intervertebral space between 4th and 5th cervical vertebrae and partial destruction, fusion and displacement of the bodies of the 4th and 5th cervical vertebrae.

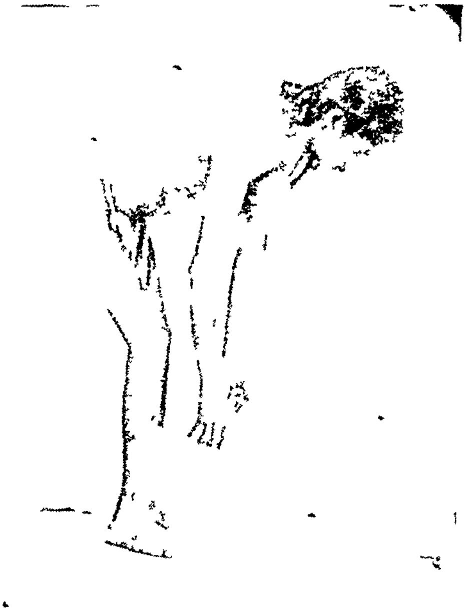

Fig. 5.—Case 10. Clinical photo of the patient showing stiffness of the back.

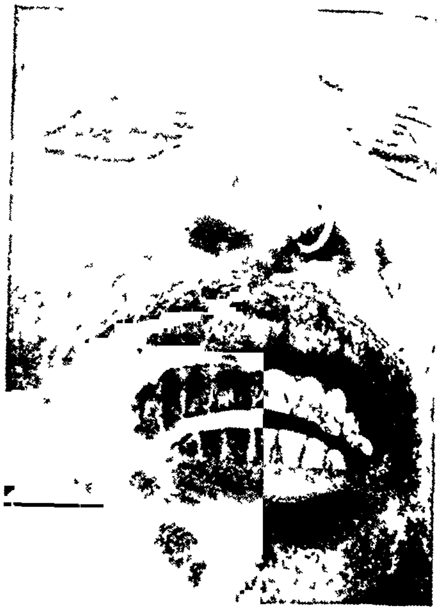

Fig. 6.—Case 10. Clinical photo showing mottling of teeth.

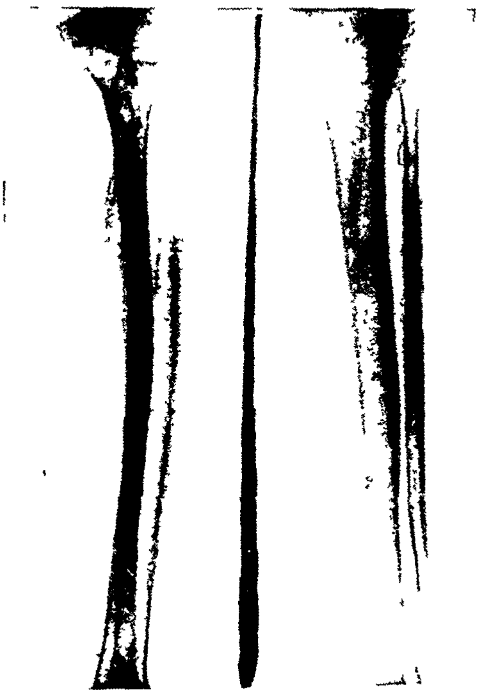

Fig. 7.—Case 10. X-ray of tibia and fibula showing extensive exostoses.

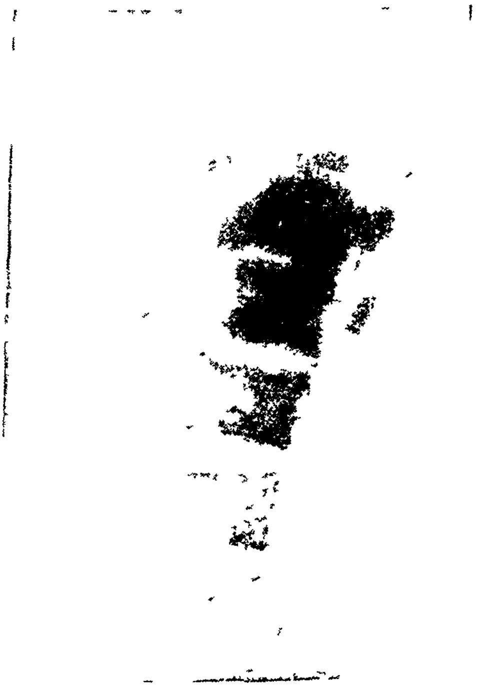

Fig. 8.—Case 10. X-ray of dorso-lumbar spine showing exostosis of the bodies of the vertebrae.

The symptoms started gradually with root pains on the right side above the right costal margin and numbness from about the level to the right leg. The disability on the left side was noticed after a fall a few days subsequent to the starting of the complaint. During the last 10 months she developed gradual inability to walk. Physical examination showed motor weakness more on the right than on the left, bilateral positive Babinski response. There was diminished sensation on both sides to all modalities below the T10 segmental dermatome level and hesitancy of micturition and defecation. The heart showed left ventricular hypertrophy and systolic murmur in the mitral was conducted to about 1″ out. The lungs were clear, urine showed no albumin and no sugar. The blood pressure was 220/120 mm. Hg. The cerebrospinal fluid was clear, under normal pressure, jugular compression was not conclusive, proteins 90 mg. and globulin +. The Wassermann reaction of cerebrospinal fluid and blood was negative. A plain roentgenogram of the spine revealed nothing abnormal but with lipiodol by the lumbar route the picture was suggestive of a block at the T4, 5 vertebral level. Taking into consideration the age and the high blood pressure, this case was not considered suitable for exploratory laminectomy for which she was also not willing.

Case 8. (Serial No. 3) :—A Hindu female of 18 years was admitted on 1-10-49 for inability to walk (one month). There was a history of fever one month prior to the main complaint. Physical examination showed spastic paraplegia with sensory loss to all modalities from below the segmental level D4 D5. There was hesitancy of micturition. The cerebrospinal fluid was clear, 40 mm. pressure; jugular compression was inconclusive, proteins 35 mg. and globulin +. The Wassermann reaction of the cerebrospinal fluid and blood was negative. Roentgenograms of the spine, plain and with lipiodol, gave no useful information. Though spinal tumour was probable in this case a laminectomy was not considered indicated. The case could not be followed.

Comment :—Though the symptomatology in case 5 was strongly suggestive of a spinal tumour the negative operation and post-mortem findings are surprising. It is possible that it was an intramedullary tumour that had been missed despite the serial sections.

In respect of case 6, a re-exploration at a lower level would appear indicated.

Cases 7 and 8 require a follow up but it has not been possible to do so.

SPINAL COMPRESSION DUE TO SYPHILITIC OSTEOPERIOSTITIS

Case 9. (Serial No. 6) :—P. M., a Muslim male aged 45 years, a jutka driver by occupation, was admitted on 2-12-49 for inability to use his upper extremities and lower extremities(20 days). He denied any history of venereal infection, and the family history did not reveal any syphilitic stigmata. There was no history of any fever. Six months previously he had been stricken with pain in the neck shooting down the upper arms for which he took some injections 20 days prior to admission. Then he noticed difficulty in walking and simultaneously experienced difficulty in flexion of the fingers of both the hands. He could not initiate the act of micturition and defecation.

Physical examination showed a bed-ridden patient who could hardly feed himself. He could be made to sit up but the movements of his head were limited. Higher cerebral functions and cranial nerves were normal. Both upper and lower extremities showed motor weakness, the fingers of both the hands were kept in a position of flexion with defective extension of the terminal and middle phalangeal joints and he had a partial claw hand. Abduction and adduction of the fingers was difficult. There was wasting of the intrinsic muscles of the hand with flattening of the thenar and hypothenar eminences. There were no fibrillations. The lower limbs were spastic with a little wasting. There were no abnormal movements. Biceps and triceps jerks on both sides were lost while the radial periosteal jerk was brisk on both sides. Ankle and patellar clonus was present on both sides and the plantar response was promptly extensor on both sides. There was hesitancy of micturition and defecation. There was a lack of appreciation to all modalities of sensations over the whole trunk, lower extremities, and both upper limbs corresponding to sensory dermatome level C6 C7 on the right and C7 C8 on the left and below. There was definite tenderness over the C5 and C6 vertebrae though there was no deformity. The cerebrospinal fluid was under normal pressure, proteins were 100 mg. globulin+. The Wassermann reaction of the cerebrospinal fluid was positive (+), and that of the blood + +. A roentgenogram of the cervical spine (Fig. 3) showed, in the anteroposterior view, increased density of the body of the 6th cervical vertebra and new bone formation on either side of the 4th, 5th and 6th cervical vertebrae. The intervertebral space between the 4th and 5th and 5th and 6th vertebral bodies appeared to be narrowed. In the lateral view (Fig. 4) the intervertebral space between 4-5 vertebrae was obliterated. The fourth and fifth cervical vertebral bodies were out of alignment and partially destroyed and fused. The patient was given 6 mega units of penicillin followed up by a full anti-syphilitic course of treatment with arsenic and bismuth supported by potassium iodide. Once the penicillin course was started the patient showed remarkable improvement and gradually regained power in the upper extremities, and the use of his hands. When he had completed another course of treatment, which was about 14-4-50, he was capable of getting up and going about the hospital and help himself. At the end of 4 months the patellar and ankle clonus disappeared and though there was still a positive bilateral Babinski response and exaggeration of the ankle jerks, the sensory changes were greatly improved but still were in defect. Two months subsequently he had another course of penicillin and anti-syphilitic treatment and was discharged at request on 23-6-51 having recovered considerably. He could go back to his vocation.

Comment :—This is a case where the compression of the cord is due to syphilitic osteoperiostitis in whom penicillin therapy as an antisyphilitic therapy has initiated a dramatic course of recovery. Supporting anti-syphilitic therapy with arsenic, bismuth and iodides was probably unnecessary but was given as a safety measure. The point would arise in these cases whether surgical interference is necessary in the form of an Albee's bone graft to support the week cervical spine.

SPINAL COMPRESSION DUE TO FLUOROSIS

Case 10. (Series No. 27) :—V. J. N. a male aged 35 years, a field labourer and Harijan by caste was admitted on 13-6-51 for inability to use both lower limbs and tingling and numbness all over the body (6 months). He has a brother and uncle who had stiff backs and was living in the Harijan colony of a village ever since his birth and used to draw his drinking water supply and that of the other members of his family from two wells to which they were restricted by caste limitations. He gave a history of a fall from a house top one year prior to admission and also 9 months later he slipped and fell on the ground, but on both these occasions he was not disabled. The present illness commenced as tingling and numbness in the left buttock and subsequently spread to the toes and back and all over the body. Due to this he had to go about with a stick for the last one month and he found himself considerably disabled. Physical examination showed that the patient walked with difficulty with a spastic ataxic gait and a stiff back (Fig. 5) which he supported with the right hand while he used the stick in the left. He had well marked mottling of teeth (Fig. 6). Motor power was poor in all the four limbs but more prominent in the legs. The tone of the upper limbs was normal while there was clasp knife rigidity in the lower limbs. The finger-nose test was well executed but the heel-knee test was badly executed on account of spasticity. Biceps and triceps jerks, + in both the upper limbs, knee jerk and ankle jerk ++ in both the lower limbs and the plantar response was extensor on both sides. There was a sensory disturbance to all modalities from below the C5 C6 segmental level on both sides. There was precipitancy of micturition while the bowels were constipated. Cerebrospinal fluid was clear and under normal pressure, proteins 40 mg., globulin +. The Wassermann reaction of blood and cerebrospinal fluid was negative. Roentgenograms of the spine and long bones showed extensive densification and also exostosis of the ribs, tibia and femur (Figs. 7-8). That of the cervical spine showed obliteration of the intervertebral space between C5 and C6 in addition to a general densification of the bodies of the vertebrae.

A field survey of the village showed that the fluorine content of the wells from which the patient was deriving his water supply was in the neighbourhood of 10-12 parts per million, while that of the other wells was only 1.3 and 1.8 parts. No treatment could be given in this case.

SPINAL COMPRESSION DUE TO COMPRESSION FRACTURE SPINE

Case 11. (Serial No. 10):—A male aged 40 years was admitted on 25-2-50 for inability to walk (9 months), following a fall from a tree and numbness below the umibilicus down to the buttock and hesitancy in micturition. Physical examination revealed wasting of both lower limbs with poor motor power; diminished deep reflexes in both lower limbs and diminution of all sensations to all modalities from about 2" below the umbilicus. The cerebrospinal fluid and blood were normal. A roentgenogram of the spine showed a compression fracture of the first lumbar vertebra.

SPINAL SYPHILIS AND DOUBTFUL SPINAL SYPHILIS

Case 12. (Serial No. 1):—A male, aged 31 years, was admitted on 15-7-51 for inability to walk (4 months). He gave a history of a sore on the penis two years ago. He was not married and the present complaint set in gradually with stiffness and weakness of legs and incontinence of urine. Physical examination at the time of admission showed spastic paraplegia unassociated with sensory disturbances. There was no incontinence of urine and no difficulty in defecation. The cerebrospinal fluid was clear and under 110 mm., pressure. Cells, 12 lymphocytes per c. mm., proteins 55 mg., globulin ++. The Wassermann reaction of the cerebrospinal fluid was ++. A roentgenogram of the spine showed nothing abnormal. He was treated with 6 mega units of penicillin, and iodides. There was no clinical improvement; he was discharged against advice.

Case 13. (Serial No. 5):—H. M., a 38 years old male was admitted on 7-12-49 for stiffness in the lower limbs and difficulty in walking of 4 months' duration. The complaint began with backache followed gradually by inability to walk. At the time of admission he had signs of spastic paraplegia. There were no sensory disturbances but he had difficulty in micturition and defecation.

The cerebrospinal fluid was clear and under normal pressure. Proteins 45 mg., globulin +, cells 18 lymphocytes per c. mm. ; he was advised antisyphilitic treatment and no further follow up could be made.

Case 14. (Serial No. 9) :—A male, aged 30 years, was admitted on 9-2-50 for complete inability to use both legs (15 days). There was a history of a sore on the penis 4 years previously and incomplete anti-syphilitic treatment. The complaint started with pain and rigidity around the waist which was followed two days subsequently by his inability to use the legs. At the time of admission he had flaccid paraplegia with a-reflexia and negative plantar response. There was a loss of sensation to all modalities from below the area midway between the umbilicus and symphysis pubis. There was no wasting of the muscles but there was incontinence of urine with distention of the bladder. The cerebrospinal fluid was clear and under normal pressure, 12 lymphocytes per c. mm., 55 mg. protein and globulin +. The Wassermann reaction of the cerebrospinal fluid and blood was +. He was advised anti-syphilitic treatment and no further follow up could be made.

Case 15. (Serial No. 21) :—A male, aged 40 years, was admitted on 16-12-50 with a complaint of inability to walk and tingling and numbness of 3 months' duration. There was a history of venereal diseases, 5 years previously. The disability came on suddenly and at the time of admission he had signs of spastic paraplegia with incontinence of urine but no objective sensory disturbances. The cerebrospinal fluid was clear and under normal pressure, 12 cells (lymphocytes) per c.mm., proteins 45 mg. globulin +. The Wassermann reaction of cerebrospinal fluid and blood + A roentgenogram of the spine showed nothing abnormal. He was advised anti-syphilitic treatment.

Case 16. (Serial No. 24) :—A male, aged 28 years, was admitted on 7-2-51 for inability to walk and tingling and numbness of lower extremities of 1 1/2 months duration. He gave a history of a sore on the penis 8 years previously. The present disability set in gradually and at the time of admission he had signs of spastic paraplegia with no sensory disturbances or sphincter disability. The cerebrospinal fluid was clear and under normal pressure, cells 12 per c.mm., lymphocytes, proteins 55 mg. globulin +. The Wassermann reaction of the cerebrospinal fluid was negative but that of the blood was strongly positive. With anti-syphilitic treatment there was slight improvement.

Case 17. (Serial No. 26) :—A male, 40 years, was admitted on 25-4-51 with a complaint of inability to walk and with tingling and numbness and weakness of right upper extremity of 4 years duration. He denied all history of venereal diseases. At the time of admission he had spastic paraplegia of the lower limbs with flexor spasms. There was poor motor power, spasticity, and hyper-reflexia in the upper limbs also but less than in the lower limbs. There was defective sensation to all modalities from about the clavicle in the thorax, and the lower limbs and on the medial aspect of the arms and forearms over the C8 T1 segments. The cerebrospinal fluid was clear and under normal pressure, cells 14 per c.mm., lymphocytes, proteins 200 mg., globulin +. The Wassermann reaction of blood was strongly positive, (++) and that of the cerebrospinal fluid was +. A roentgenogram of the spine was normal. Improved slightly under anti-syphilitic treatment.

Case 18. (Serial No. 19) :—A male, aged 38 years, was admitted on 16-9-50 with inability to use lower limbs (8 months). There was a history of a sore on the penis 3 years previously. His wife had an abortion and a number of still births. The complaint started with weakness of the right leg which gradually extended to the right upper limb and then left upper limb and later left leg. There was no dysphagia and no alteration of voice. At the time of admission, the cranial nerves and speech were normal. There was high stepping gait with foot drop on both sides, more on right than on left. Motor power was poor in all the limbs, deep reflexes were exaggerated in all limbs, and the plantar response was extensor on both sides. There were no sphincter disturbances and no sensory disturbances. There was, however, wasting of the small muscles of the hand with claw hand on both sides and fasciculation of wasted muscles. Cerebrospinal fluid was clear and under normal pressure, no cells, protein 12 mg., globulin, a trace. The Wassermann reaction of the cerebrospinal fluid was negative while that of the blood was +. A course of anti-syphilitic treatment gave no relief.

Comment :—These are cases where there is either an antecedent syphilitic history or the serology of blood and the findings of the cerebrospinal fluid are incriminating. In all these cases anti-syphilitic treatment is certainly indicated and may or may not show clinical improvement. But even in these cases the possibility of a compression lesion of the cord should not be lost sight of. The syphilitic history and positive serology should not cloud the issue of a spinal tumour.

PARAPLEGIA PROBABLY OF TOXIC INFECTIVE ETIOLOGY

Case 19. (Serial No. 2) :—A male aged 20 years, was admitted on 13-1-49 for inability to walk and weakness of the legs of 1 1/2 years duration. There was a history of prolonged fever of one month's duration following which the present complaint started. There were signs of spastic paraplegia with a lack of appreciation of touch on the left leg in the region of L4 and L5 segment, otherwise no sensory disturbances and no sphincter disturbances. The cerebrospinal fluid and blood, and spine roentgenogram were normal. He was advised physiotherapy and re-education exercises.

Case 20. (Serial No. 23) :—A male child aged 6 years, was admitted on 3-2-51 for inability to walk (20 days). There was a history of continuous fever of 25 days preceding the complaint. At the time of admission he had signs of spastic paraplegia but there was no sensory disturbance or sphincter disability. Cerebrospinal and blood Wassermann reactions were normal. No follow up could be done.

Case 21. (Serial No. 29) :—A male aged 37 years, was admitted on 5-7-51 with inability to walk (4 months). The complaint started with a burning sensation in the lower limbs (15 days) and subsequently he had fever for 20 days which resulted in stiffness and weakness of the lower limbs. At the time of admission the patient had signs of spastic paraplegia with diminished sensation to all modalities over the soles of the feet. There was precipitancy of micturition and defecation. The cerebrospinal fluid was clear and under normal pressure, one cell per c.mm., proteins 5 mg., globulin nil, cerebrospinal and blood Wassermann reactions were negative. A roentgenogram of spine showed nothing abnormal. No follow up was possible.

SPASTIC PARAPLEGIA DUE TO SUBACUTE COMBINED DEGENERATION OF THE CORD

Case 22. (Serial No. 15) :—A male, aged 35 years, was admitted on 24-6-50, for inability to walk with tingling and numbness of extremities of 8 months' duration. The family and previous history were not contributory. The present complaint started with tingling and numbness of the lower extremities with increased stiffness and difficulty in walking. At the time of admission there were signs and symptoms of impairment of the lateral and posterior columns in the lower limbs, with a glove and stocking type of anesthesia, but there were no sphincter disturbances. Blood examination showed 4.2 million red cells, 11.7 Gm. Hb. (Sahli), P.C.V. 35, mean corpuscular volume 85 cubic microns (Normal 87 c. u) and mean corpuscular hemoglobin concentration 33.5 per cent (Normal 35%). The peripheral blood smear was normocytic, Van den Bergh reaction negative ; sternal puncture was normal, and the fasting test meal showed histamine fast achlorhydria.

Case 23. (Serial No. 20) :—A male, aged 30 years, was admitted on 1-11-50 for inability to walk (4 years). There were no root pains or subjective sensations of tingling and numbness. There were signs of spastic paraplegia and definite impairment of vibration sense, in both lower limbs. There were no sphincter disturbances.

Cerebrospinal fluid and blood were normal. Hematology showed microcytic and hypochromic anemia. A fasting test meal showed histamine fast achlorhydria.

Comment :—The common impression that subacute combined degeneration of the cord is usually associated with anemia is wrong as borne out by these cases. Histamine fast achlorhydria on the other hand is a significant feature that clinches the diagnosis.

SPASTIC PARAPLEGIA DUE TO AMYOTROPHIC LATERAL SCLEROSIS

Case 24. (Serial No. 17) :—A Hindu male aged 22 years, was admitted on 16-8-50 for difficulty in walking and weakness of the hands and muscular twitchings of two months duration. A younger brother too has a similar complaint. He had slurring speech but no wasting ; there were fibrillations over the tongue. There were no sensory or sphincter disturbances, but there was obvious wasting of the small muscles of the hand with muscular twitchings. There was hyper-reflexia in both upper and lower limbs with prompt bilateral positive Babinski responses. The blood and cerebrospinal fluid were normal.

SPASTIC PARAPLEGIA DUE PROBABLY TO LITTLE'S DISEASE

Case 25. (Serial No. 25) :—A Hindu male child aged 10 years, was admitted on 29-5-50 for inability to walk since birth. There was no significant obstetric or family history, the child was said to have been well till about the 10th month when he had some fever for a week and the disability in walking was noticed. The child manifested a typical scissor gait with spasticity of the lower limbs. The upper limbs showed hyper-reflexia though the tone and motor power were normal. There were no sensory or sphincter disturbances. The cerebrospinal fluid and roentgenogram of the spine and skull were normal.

PARAPLEGIAS OF UNKNOWN ETIOLOGY

Case 26. (Serial No. 4) :—A Hindu female aged 20 years, was admitted on 29-8-49 for inability to walk and weakness of the right upper limb for one year's duration. There was a history of a fall from a small height previous to the complaint but the patient was not unconscious after the fall. There has been a history of headache and vomiting before the onset of the complaint. There was spasticity of the lower limbs more marked in the right than on the left. There was hyper-reflexia in all the limbs. There was papilledema, but no sensory and sphincter disturbances. The cerebrospinal fluid and blood were normal. Roentgenograms of the spine and skull were normal, encephalography and ventriculography were not contributory.

Case 27. (Serial No. 13) :—A male aged 48 years, was admitted on 19-4-50 for difficulty in walking of 3 months duration. There was spastic paraplegia of the lower limbs with no sensory and sphincter disturbances. Cerebrospinal fluid and blood were normal.

Case 28. (Serial No. 16) :—A female of 25 years, was admitted on 16-8-50 with inability to walk and dribbling of urine of 1 month's duration. She was married but sterile and had no abortions. There were signs of spastic paraplegia but no sensory and sphincter disturbances ; Cerebrospinal and blood Wassermann reactions were normal. Roentgenograms of the spine did not reveal any abnormality.

Case 29. (Serial No. 18) :—A female aged 20 years, was admitted on 23-8-50 for inability to use the lower limbs with tingling and numbness of one year's duration. She was married and sterile, had had no abortions and noticed a burning sensation of the soles of feet then, tingling and numbness, and later stiffness and diffculty in walking. There were signs of spastic paraplegia but no sensory disturbances. Difficulty in initiating micturition and defecation was present. The cerebrospinal fluid and blood were normal ; A roentgenogram of the spine was normal.

Comment :—These cases were discharged as paraplegias of unknown etiology. No follow up was possible but it is in such cases that a prolonged follow up is essential to determine the pathological diagnosis as it is not improbable that some of these may turn out to be cases of spinal tumour that may improve by operative interference.

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The Legend on Cesarian Section

Al Biruni, an Arab physician and scholar who lived in the tenth century, A. D., is the author of many books on medicine history and astronomy. One of his most interesting books states that the mother of Caesar Augustus died in labor and her abdomen was cut open and the child delivered through the wound. He also mentions another instance where a certain Ahmed Ibn Sahl was delivered in a similar manner, but he does not mention that any other cesarian operation occurred during his lifetime. although Al Firdawsi, his contemporary, relates that Rustom, the son of Zal, was delivered by a Cesarian operation performed on his mother, Rudaba. In his Shah Nama, which he wrote in Persian, Al Firdawsi relates a very interesting story which tells how a bird sent from God appeared to Zal and told him to secure an able physician who would drug Rudaba to sleep and, with a sharp iron, open her side, deliver the baby, and suture the incision, which when touched with a feather from his wing would recover immediately, and thus will bring all their anxiety and sorrows to an end.

Whether these be legends or bases on facts, it is enough to show that the Orient was aware of the cesarian operation, which was used not only with the aim of getting a living baby, but with the sincere hope of saving the mother's life as well. From the First Annual Report of the Orient Hospital, Bierut, Lebanon. Quoted from American Practitioner, 2: 807, 1951.

GRADING OF TUMORS

A REVIEW

M. V. Sirsat *

One of the main problems in cancer that confronts both the clinician and the pathologist alike is the prognosis. The literature on this subject is so vast and varied, and presents such complex and baffling material that the task of a reviewer is by no means easy. An attempt has been made here to review the present state of knowledge regarding the methods of microscopic grading and its significance in the prognosis of cancer. It is not claimed that all aspects of the subject have been adequately dealt with.

Virchow,[74] who laid the foundations of cellular pathology, it appears, was well aware that different groups of cancers varied in the degree of their malignancy. Hansemann[30], however, was the first to point out the relationship between their histologic structure and clinical behaviour. He also showed the value of recognising grades of clinical malignancy on the basis of degree of histologic abnormality. The term 'anaplasia', (backward to form) meaning loss of differentiation and increase in the reproductive power in a tumor, was introduced by him. He maintained that the production of metastasis by a tumor was directly related to anaplasia: the greater the anaplasia, the greater was the tendency to give rise to metastasis.

The histologic criteria of anaplasia are based on the cellular characters such as variation in size and shape of nuclei, nuclear hyperchromatism, number of mitotic figures and atypical quality of mitosis, infiltrative tendencies, loss of polarity and absence of adult differentiated characters. It is by these cytologic features that the growth capacity and potential malignancy of a tumor are judged. But, in the final analysis, the factors which determine the degree of malignancy are the biologic characters of the cancer cells and, therefore, prognosis in cancer is essentially based on the manner in which the protective forces of the organisms are functioning. [41], [46], [47], [48], [49], [58].

Ewing[19] established that a pathologic diagnosis, simply as a carcinoma or a sarcoma, was inadequate. He suggested that the potential malignancy of a tumor could be judged accurately from its histologic structure, but its actual clinical course might be subject to wide variations, depending chiefly on location, size and presence of metastasis.

The behaviour of carcinomas in different organs of the body is known to vary. Besides, different kinds of carcinomas behave differently. For instance, a squamous cell carcinoma is known to be more

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malignant than a basal cell carcinoma ; a melanoma of the skin is known to be more malignant than either a basal cell or a squamous cell carcinoma. A squamous cell carcinoma of the cervix is known to be of higher average malignancy than a suqamous cell carcinoma of the lip, and an adenocarcinoma of the stomach is known to be of higher average malignancy than an adenocarcinoma of the body of the uterus. With regard to carcinomas of the same type at the same site, the difference in malignancy was not recognized until Broders'[7], [8] pioneer work in the field of grading of tumors. Broders' work aroused interest in surgeons and pathologists, by his statement, that the clinical course of many carcinomas might be fairly accurately predicted by an analysis of the histologic structure alone, without taking the clinical features into consideration. His thesis was based on Hansemann's law that the more highly differentiated the cells of a tumor the lower was its malignancy. Broders[5],[6] published his first paper on the grading of carcinoma of the lip in 1920 and, a year later, he came out with a second one pertaining to tumors of the skin. He divided these carcinomas into 4 grades, each representing the degree of differentiation of the tumor cells, and presented statistics to prove that these histologic features bore a definite relation to the life expectancy in any particular case. The grading depended upon the following criteria. If a given tumor revealed one-fourth of its cells to be poorly differentiated and the rest well differentiated, it came under grade I; if it showed one-half of the cells in each group, it was in grade II ; if three-fourths of the cells were poorly differentiated, it was placed in grade III: and, lastly, if all of them were poorly differentiated, it fell in grade IV. By this method, Broders revealed a close relationship between the degree of anaplasia, as judged by these numerical grades and the length of survival, and showed that with decreasing differentiation there was increasing malignancy.

At present, the most reliable information in regard to prognosis of malignant tumors is obtained by judicious evaluation of the histologic structure along with consideration of the clinical extent of the disease. The purpose of this review is to analyse the possibilities and limitations of microscopic grading in the prognosis of cancer. Where clinical factors are of greater significance in prognosis, due emphasis will be given to them. The method adopted is to discuss individual cancers. The discussion is restricted to cancer of the breast, uterus, rectum, thyroid, urinary bladder, prostate, bone and brain.

CARCINOMA OF THE BREAST

The histologic features, which have been chosen as the basis for grading carcinoma of the breast, have varied with different authors[21],[34]. Haagensen[29] investigated as many as fifteen different factors falling broadly under three main groups : (1) manner of growth, (2) cell morphology and (3) stromal reaction. He concluded that histologic grading was simply an additional prognostic guide and should be subordinated to the clinical data. Harrington[31, 32] in a clinicopathologic study, graded a large number of breast carcinomas. His conclusion was that the histologic grade of malignancy quite accurately indicated the expected survival period, especially when considered together with the state of the axillary glands.

The system of grading that seems to help most in judging the prognosis is the one suggested by Greenough[27], in which the chief histologic characters considered are the adenomatous structure, tubule formation, secretory activity, variation in the size of the cells and nuclei, hyperchromatism and mitotic figures. Originally, his classification included four groups : (1) a group in which there was definite differentiation, (2) one with moderate differentiation, (3) one with slight differentiation and (4) a group containing the highly malignant forms. Later, only three groups were established : tumors of low, moderate and high malignancy (groups 1, 2 and 3 respectively). Greenough[27] considered the presence of mucoid droplets in tumor cells as a good indicator of lower malignancy ; it signified secretory activity and, therefore, meant cell differentiation. Delbet and Mendaro[15], and Frantz[23] agreed with this view ; in their opinion the presence or absence of mucus secretion was the most important factor in ascertaining the outcome in patients with mammary carcinoma. According to Greenough[27], the size of cells and nuclei were by themselves unimportant, but variability in size indicated high malignancy. Colloid carcinoma of the breast found no place in Greenough's classification, perhaps on account of its relative rarity. Colloid carcinomas are of low grade malignancy, slow in growth and the involvement of axillary nodes is either rare or late. These are the chief characters referred to in the descriptions of gelatinous carcinoma of the breast [11, 25, 43, 61].

Greenough[27] contended that, in carcinoma of the breast, the degree of malignancy could be determined with reasonable accuracy by a study of the histologic picture. The principles laid down by Greenough[27] were employed by others such as Smith and Barlett[11], Simmons *et al.*[67], Patey and Scarff,[56, 57] and Scarff and Handley[62]. In the opinion of these authors, the method of grading suggested by Greenough[27] had definite

TABLE 1.—*Histologic Appearance and Clinical Course in Carcinoma of the Breast.*

Grade.	Cases.	No. alive after 5 years.
I	16	11
II	12	5
III	22	5

value in indicating the likely prognosis in patients suffering from carcinoma of the breast. Tables 1, 2, and 3 are incorporated to show the relationship of grades, as suggested by Greenough[27], to the prognosis in carcinoma of the breast. Patey and Scarff[57], in a series of 50 cases (Table 1), showed that there was a definite correlation between the histologic appearance and clinical course. In a further study of 172 cases (Table 2), Scarff and Handley[62] found that the main criteria of value were de-differentiation and evidence of rapid growth. These authors, however, pointed out that, although grading was of importance, the clinical stage which the disease had reached was of far greater significance as far as the ultimate prognosis was concerned. This, of course, by no means denies the importance of histologic grading, because the presence of metastasis depends to a considerable extent on the histologic type of the growth and, highly malignant growths show a higher percentage of cases with secondary deposits in the lymph glands at the time of operation[63]. The relationship between the degree of malignancy and occurrence of metastasis in carcinoma of the breast is well illustrated by Patey and Scarff[56] (Table 3).

TABLE 2.—*Grading and Prognosis in Carcinoma of the Breast.*

Grade.	Cases.	Number alive.	
		After 5 years.	After 10 years.
I	62	27 (45%)	19 (31%)
II	66	19 (29%)	7 (11%)
III	44	10 (23%)	6 (13%)
Total	.. 172	56 (33%)	32 (19%)

TABLE 3.—*Histological Malignancy and Metastasis in Carcinoma of the Breast.*

Histological Grade of Primary.	Total No. of cases.	No. with Metastasis.	No. without Metastasis.
I Low malignancy	54	24	30
II Moderate malignancy	57	39	18
III Marked malignancy	52	47	5

The clinical factors that play a role in prognosis are : presence of lactation, rate of growth and extent of the disease. Carcinoma of the breast, associated with pregnancy or lactation, usually runs a rapid course. Similarly, involvement of the axillary lymph nodes alters the prognosis even in early cases [42], [68], [69], [73]. Besides grading, therefore, these factors should be taken into account when one estimates the prognosis. Bloom[3] studied 470 cases of mammary carcinoma, and found that, the grade of the tumor taken together with the state of the axillary lymph nodes, gave a more accurate indication of the outcome than either of these factors alone.

CARCINOMA OF THE CERVIX UTERI

Schottlaender and Kermauner[64] were among the first to divide epidermoid carcinomas of the cervix into three histologic grades to which they applied the terms mature, half mature and immature. This division was based upon the degree of anaplasia. Broders[9] separated the same tumor into grades I, II, III and IV, in the order of decreasing differentiation and increasing malignancy. Later, Martzloff[51] established a grading for cervical carcinoma upon the same fundamental principle of loss of differentiation or anaplasia. He did not employ a numerical system but divided carcinoma of the cervix into four types : adenocarcinoma (endocervical), spinal cell carcinoma, transitional cell carcinoma and spindle cell carcinoma. The spinal or prickle cell variety is composed, for the most part, of cells resembling those seen in the superficial zone of the normal stratified cervical epithelium. The cells are adult in character and exhibit their tendencies by the formation of cell nests or pearls. Mitotic figures are few. The transitional cell variety is composed of cells resembling the midlayer of the stratified cervical epithelium. The cells have variable shapes and are often round. The cytoplasm is relatively sparse. The spindle cell variety is composed of spindle shaped cells. In this variety mitotic figures are common. The cytoplasm is very sparse and the cells are closely packed. Based on these cell types, Martzloff[51] concluded that the spinal cell type tumor was the least malignant form in the cervix, the spindle cell type the most malignant, while the adenocarcinoma and tumors composed of transitional cells occupied an intermediate position. In a subsequent publication, Martzloff[52] observed that, in carcinoma of the cervix uteri, biopsy failed to indicate correctly the predominant type of cancer cell in the parent tumor in one-third of the cases. Borges[4] had a similar experience ; he reported that, in 33 per cent of the cases studied by him after radical hysterectomy, the lesion as a whole was different from that indicated by the biopsy. Quite pertinently, therefore, has Martzloff[52] asserted that, if biopsy alone were relied upon to determine the predominant cell type and the results so obtained utilised in suggesting prognosis, the conclusion may be wrong. At the Tata Memorial Hospital, Bombay, Martzloff's method was applied in biopsy of 300 cases of cervical carcinoma[39]. It was found that this series was comparable to that published by Jones[36] from the Kelly Clinic. (Table 4).

Martzloff[52], himself, called attention to the marked histologic similarity between his spinal, transitional and spindle cell types and

Broders'[9] grades II, III and IV, respectively ; also, he pointed out the close agreement between his figures, concerning surgical cases in their relation to the predominant cell type, and those obtained at the Mayo Clinic,[52] where Broders' histologic classification was followed. Martzloff's findings indicated that, when treated surgically, the spinal cell type had the best prognosis and the spindle cell type the worst. His conclusion, as to the graded malignancy of these various cell types of cervical carcinomas, were based on a study of 203 cases submitted to surgery at the Johns Hopkins Hospital. Of the patients that he was able to trace, 26 per cent were found to be free of the disease five years after the operation. Of these, in 47 per cent, the removed tumor was composed predominantly of the spinal cell type; in 24 per cent, of the transitional cell type; and, in only 10 per cent, of the spindle cell type. From this investigation, Martzloff concluded that the determination of the cell type in epidermoid carcinoma of the cervix was important, in that it indicated the relative malignancy of a given tumor: the spinal cell type was the least malignant and the spindle cell type the most malignant. It seems that, though reliable histologic division is possible, there is no correlation between the degree of malignancy and radiosensitivity or curability, as expressed in terms of five-year cures. This is because there are many other factors involved: factors, such as the size, form, gross extent and morphologic type of the tumor, which are quite definite and far more important than the cell type. At the present time, two systems of recording the anatomic spread of the disease are in vogue; they are the Schmitz[66] system and the League of Nations[78] system.

TABLE 4.—*Percentage Distribution of Cervical Carcinoma According to Cell Type (Martzloff).*

	Spinal cell type.	Transi- cell type.	Spindle cell type.	Adenocarcinoma.	Total.
Kelly Clinic	6	77	13	4	704
T. M. H.	10	72	16	2	300

A reference may be made to two morphologic types of carcinoma of the cervix to which Ruge and Viet[60] have drawn attention, namely, the everting and inverting types. The everting or cauliflower form of growth was thought to be less malignant. The inverting type produced an enlargement of the cervix as a whole, was more likely to ulcerate and infiltrate the parametrial tissues and, hence, was considered a more malignant form. Galvin[24] stated that such a morphologic division, although at times helpful in the estimation of prognosis, did not meet the exacting requirements of a basic grouping of cervical carcinomas.

CARCINOMA OF THE BODY OF THE UTERUS

Kaufman[38] divided carcinoma of the uterus into several histologic varieties. First, the adenoma malignum, which is characterised by a well differentiated cell pattern with predominance of acinar tissue and scanty stroma. The second type, the usual form of adenocarcinoma of the fundus, is characterized by areas where the carcinomatous nature of the tumor is evident. The cells show marked variability in size and are seen arranged in typical acinar formations. The stroma is moderate in amount and seen to interperse between the acini. The third group is the papillary adenocarcinoma. In this, the glandular epithelium is sparse and rests on a fibrovascular core of connective tissue. The fourth group, Kaufman called adenocarcinoma solidum; in this, there are large sheets of undifferentiated cells and only a few areas with acinar arrangement. The most interesting type is that which covers the entire mucosa as a squamous cell carcinoma without acinar formation. The underlying tissues may be infiltrated with small celled carcinomatous projections and the surface may be papillary. Mahle[50] graded carcinoma of the body of the uterus in a manner similar to Broders'[5], [6], [7] method of grading. He stressed that a tumor with a high degree of malignancy and low cellular differentiation grew larger and invaded more extensively in the same interval of time than a tumor with a lower degree of malignancy and high cellular differentiation.

Mahle's[50] conclusion, from a study of 186 cases of carcinoma of the body of the uterus, was as follows : (1) The accepted belief of a relatively favourable outlook for carcinoma of the body of the uterus in comparison to carcinoma of the cervix had a pathologic basis, in that, in the former, the number of cases which showed a high degree of differentiation were in the majority. (2) The longest survival period since operation, of those patients who were dead in the series, was in cases of grade II malignancy and the shortest in grade IV.

CARCINOMA OF THE RECTUM

The histologic criteria for grading carcinoma of the rectum, once again, are based on Broders', [5], [6], [7] classification of malignant tumors. The malignancy of carcinoma of the rectum, again, appears subject to gradation on the fundamental principle of cell differentiation. In grade I, the tumor closely resembles an adenoma but shows active epithelial proliferation. In grade II, the tumor cells are crowded together but still arranged in a fairly regular fashion, one to two layers deep and around glandular spaces. The nuclear material stains deeply and irregular mitotic figures are commonly seen. Grade III tumors are less differentiated. The cells lining the glandular spaces are often two or three layers deep or they form solid clumps. Mitotic figures are more numerous than in grade II carcinoma. In grade IV, the tumor cells are even more anaplastic ; these do not form glandular structures but infiltrate the tissues singly or in small irregular groups and clumps[17].

Bankin and Broders[59], in a study of 598 cases of carcinoma of the rectum, graded the malignancy in accordance with Broders' method[5,6,7]. They observed that the percentage of cases in which metastasis was present was in direct proportion to the rising grade of malignancy, and, that the absence of metastasis increased in inverse proportion to it. Their study showed that in grades I and II, the end results of surgical treatment were relatively good, but grades III and IV proved increasingly malignant with a high rate of metastasis. Dukes[17] (Table 5) reported the results of a study of 985 cases of rectal carcinoma, graded according to Broders' method[5], [6], [7]. He found a close connection between the histologic grade and the extent of local spread.

A method of measuring the local spread has been devised by Dukes[17]. He divides all the 1000 cases studied into three groups—A, B and C. In the group "A" the growth is confined to the rectal wall, there being no extension into the perirectal tissue and no metastasis in the lymphatic glands. In the group "B" are cases, in which the growth has spread by direct continuity into the perirectal tissues but the lymphatic glands are free from metastasis. Cases are classified as belonging to group "C" if lymphatic metastasis are found.

As expected, a close connection was found by him between the histologic grade and the extent of the local spread. Histolgic grading, therefore, may be regarded as an approximate method of assessing the pace of growth of a tumor and, the A, B and C classification as a measure of the distance reached by the tumor. The two methods are, luckily, interrelated, as seen in Table 5 ; the group "A" cases (limited to rectal wall) contain the largest percentage of grade I growths (slow-growing tumors), whereas the group "C" cases (with metastasis) contain the highest percentage of the more malignant grades.

TABLE 5.—*Relation of Extent of Spread to Histological Grade* (985 *Cases—Dukes*).

	Grade I.		Grade II.		Grade III.		Grade IV.		Colloid.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
144 A cases ..	28	19.4	97	67.4	8	5.5	0	0	11	7.7
342 B cases ..	20	5.8	233	68.1	57	16.7	1	0.3	31	9.1
499 C cases ..	16	3.3	232	46.4	159	31.8	13	2.7	79	15.8

Colloid carcinomas of the rectum are generally regarded as a group with a very bad prognosis. Dukes[17] found that nearly all of those which survived were originally grouped as A or B cases. It appears that the important prognostic feature in colloid carcinomas is the extent of the growth and not the presence of colloid degeneration. Colloid carcinoma also vary considerably in the degree of differentiation. Like colloid carcinoma of the breast, it is difficult to establish a satisfactory standard for grading them and so they are all grouped together separately.

CARCINOMA OF THE URINARY BLADDER

Several authors have emphasised the variability in the histologic pattern in tumors of the urinary bladder[1], [33], [65], [70]. Papillomas of the bladder, even though they may appear benign under the microscope, should be considered potentially malignant. The difficulty of grading carcinomas of the bladder, therefore, is obvious; more so, because, the mortality rate of the more differentiated type is practically the same as that for the less differentiated varieties. In view of this, the Registry of the American Urological Association has suggested a method of grading carcinoma of the urinary bladder, which is a combination of clinical features and histologic characters[14]. The simplified grading proposed by the Registry is as follows :—Grade I : All papillary carcinomas, in which there is no clinical evidence of infiltration and in which no obvious infiltration of the pedicle or bladder wall can be demonstrated on histologic examination. Grade II : (*a*) *Papillary and Infiltrating Carcinoma* : infiltrating papillary carcinoma in which the papillary structure is recognizable but most of the cells are atypical in appearance and arrangement. (*b*) *Infiltrating Carcinoma* : non-papillary squamous cell carcinomas, in which the cells are fairly uniform in size and type or have a tendency to form epithelial pearls. Grade III: *Non-papillary Infiltrating Carcinomas* : very anaplastic infiltrating car-

TABLE 6.—*Five Year Survivors with Systematic Roentgen Therapy.*

Composite Grade.	Cases.	Five Year Survivals.		Cases with Systematic Roentgen Therapy.	Five Year Survivals with Roentgen Therapy.	
		Number.	Per cent in each Grade.		Number.	Per cent in each Grade.
Grades I—II ..	20	11	55	5	4	80
Grade III ..	62	26	42	12	8	67
Grade IV ..	18	1	5.6	3	1	33
Total ..	100	38		20	13	8

cinomas; practically all the cells are atypical in appearance and there is only slight or no cellular differentiation. Table 6 shows the five year survival of cases, based on the grade suggested by the Registry[14].

CARCINOMA OF THE PROSTATE

Carcinoma of the prostate has not been adequately studied from the point of view of grading. Kahler[37] studied 24 cases and divided them into 4 grades, according to Broders'[5], [6], [7], system of grading. Ferguson[20], in a study of 501 cases, divided them into three grades. Besides the histologic appearance, he took into consideration the following factors for deciding the grade : age, duration of symptoms and extent of the disease. Evans *et al.* [18], studied 100 cases and selected eight chief aspects of the tumor structure in determining the grade ; these were : (1) acinar structure, (2) cell structure, (3) density of cytoplasm, (4) nuclear characteristics, (5) presence of nucleoli, (6) mitotic figures, (7) fibrosis and (8) inflammatory exudate. The distribution of the 100 specimens according to a composite grade, as obtained from a study of all the eight factors mentioned above, was 2, 18, 62 and 18 of the tumors in grades I, II, III and IV, respectively. The authors observed that histologic grading of carcinoma of the prostate, based on the degree of abnormality of the acini, cells and nuclei, is of great value in predicting the probable length of the survival period, and also indicated the probability of the occurrence of metastasis. An analysis of Table 7 reveals that the five-year survivors are distributed in relation to the grades. It is obvious from the table that the five-year survivals are increased in the group which had the benefit of radiation therapy. This is particularly notable in grade III.

TABLE 7.—*Carcinoma of the Urinary Bladder : Cases Operated Upon More Than 5 Years Ago.*

Grade.	Cases.	Dead.	Per cent.
I	133	72	54.13
II	194	144	74.27
III	244	210	86.06
IV	70	67	95.71
Total	641	493	76 91

CARCINOMA OF THE THYROID

Carcinomas of the thyroid produce a strikingly variable histologic pattern. Because of its variability in structure, there is no demonstrable relationship between the clinical course and the pathology of thyroid malignancy. It is probably because of this that many workers have confined themselves to the study of histologic type of thyroid carcinomas[12, 28, 54, 75, 77]. Haagensen[28] classified carcinoma of the thyroid into five types : (1) papillary cystadenocarcinoma; (2) small alveolar (Hurthle cell) carcinoma; (3) adenocarcinoma; (4) giant cell carcinoma; and (5) small round cell carcinoma. This, though not directly comparable to numerical grading, has the same fundamental significance, since it is based on the principle of anaplasia. Haagensen[28], in a study of 30 cases, showed that each of the above types had a fairly characteristic natural history, especially with reference to the reaction to radiation. This he studied from the point of view of regression of the primary growth. The data obtained by him indicated a moderate radiosensitivity of the less anaplastic types of thyroid carcinoma and, that the rapidly growing anaplastic type appeared to be uniformly radioresistant. This finding is not in agreement with the law of radiosensitivity proposed by Bergonie and Tribondeau[2], according to which, the anaplastic tumors in contrast to the more differentiated types, shrink markedly after irradiation. Warren[75] has suggested a classification (see Table 8)

TABLE 8.—*Classification of Malignant Tumors of the Thyroid Gland.*

1. Low grade malignancy.
   - (*a*) Adenoma with blood vessel invasion.
   - (*b*) Papillary cystadenoma.
     (*a* and *b* are frequently grouped together)
2. Moderate grade of malignancy
   - (*a*) Papillary adenocarcinoma.
   - (*b*) Alveolar adenocarcinoma.
   - (*c*) Hurthle cell carcinoma.
3. High grade malignancy
   - (*a*) Small cell or carcinoma simplex.
     (compact and diffuse type)
   - (*b*) Giant cell carcinoma.
   - (*c*) Epidermoid carcinoma.
   - (*d*) Fibrosarcoma.
   - (*e*) Angiosarcoma.

which seems practical as it embraces correlation of certain types of clinical behaviour with certain morphologic entities. It is now used by the American Goitre Association and is widely accepted. The histologic diagnostic criteria of thyroid carcinoma are somewhat in a fluid state. Blood vessel invasion is the most important feature in identifying a thyroid carcinoma. The malignant adenoma and papillary carcinoma are the most common types of thyroid carcinoma, and the clinical course of these tumors is in keeping with their low histologic grade.

TUMORS OF THE BONE

So far the methods of grading as applicable to epithelial tumors have been discussed. There have been attempts to extend grading to certain connective tissue tumors also. Grading has been found most useful in determining the prognosis in giant cell tumors of the bone and the osteogenic sarcomas.

GIANT CELL TUMOR

The giant cell tumor of the bone, though originally benign, shows a tendency to undergo malignant change. The treatment, naturally varies according to whether such a change has occurred or not. Jaffe[35] stated that, in addition to making a diagnosis of giant cell tumor, one should attempt to grade the lesion with a view to predict its clinical course and determine the appropriate therapy. The system of grading suggested by him relates mainly to the stromal cell component of the neoplasm. Those classified as grade I are the least aggressive; in this, the stromal cells are not compact and do not exhibit any appreciable atypical characters. The tumors of grade II possess a very compact cellular stroma, the stromal cells show definite evidence of atypism ; they tend to recur and, in some cases, eventually undergo malignant transformation. Those of grade III represent the small group which possess a sarcomatous type of stroma ; these are malignant and metastasize. During the past 10 years (1941-1950) 41 cases of giant cell tumors of the bone were studied at the Tata Memorial Hospital and graded according to Jaffe's method. 17 cases fell in grade I, 21 in grade II and 3 in grade III.

OSTEOGENIC SARCOMA

Coley and Pool[13] suggested a microscopic grading of osteogenic sarcoma and emphasised its importance in determining prognosis. The grading of malignancy, as proposed by them, depends on a number of factors :—(1) The gross pathologic picture, especially the presence or absence of invasion of the epiphysis ; (2) Whether the tumor is medullary, periosteal or both ; and (3) Whether adjacent soft parts are involved. The extension of the tumor for a considerable distance in the narrow cavity, invasion of the femoral vein and extensive infiltration of soft parts are of extremely unfavourable significance. Microscopically, the grade of malignancy is determined by uniformity or pleomorphism of the cell type. Coley and Pool[13] found that, of 36 cases with tumors of low grade malignancy, 40 per cent survived for five years; of 98 with tumors of average grade malignancy, 16 per cent survived for five years ; and of 26 with highly malignant tumors, only 15 per cent survived for five years.

TUMORS OF THE BRAIN

Recently, the numerical method of grading has been extended to gliomas of the brain. Embryologically, the neural tissue is neither epithelial nor mesothelial but neuroectodermal in origin. The grading of tumors of such origin, like that of the epithelial tumors, is based on the concept of anaplasia. *Gliomas* :—A classification of the gliomas (Table 9), based on the concept of anaplasia, has recently been suggested by Svien *et al*[72]. It conceives that the neural tissue of the brain is made up of four different types of cells, from which four types of gliomas seem to arise. Medulloblastoma has been included because of its relatively constant histologic structure and common occurrence. In a study of 161 cases of cerebral astrocytomas and 57 of intracranial ependymoma, the authors report that the grade of malignancy is related closely to the average pre-operative duration of symptoms and the average post-operative survival rates. Grade I malignancy is characterised by cells of relatively normal appearance without anaplasia. In grade II, there is early anaplastic transformation of a few cells but no mitotic figures are present. Grade III is characterised by moderate anaplastic transformation of about half the number of cells and mitotic figures are present in about every other high-power field.

TABLE 9.—*Suggested Modification of Classification of Gliomas.*

New.	Old with New in Parenthesis.
Astrocytoma, grade 1 to 4	Astrocytoma (astrocytoma, grade 1) Astroblastoma (astrocytoma, grade 2). Polar spongioblastoma (obsolete). Glioblastoma multiforme (astrocytoma, grades 3 and 4.)
Ependymoma, grade 1 to 4	Ependymoma (ependymoma, grade 1). Ependymoblastoma (ependymoma, grade 2 to 4). Neuro-epithelioma (obsolete). Medullo-epithelioma (ependymoma, grade 4).
Oligodendroglioma, grade 1 to 4	Oligodendroglioma (oligodendroglioma, grade 1). Oligodendroblastoma (oligodendroblastoma, grade 2 to 4.)
Neuro-astrocytoma, grade 1 to 4	Neurocytoma Ganglioneuroma Gangliocytoma Ganglioglioma (Neuro-astrocytoma, grade 1). Neuroblastoma Spongioneuroblastoma Glioneuroblastoma and others (Neuro-astrocytoma grade 2 to 4.)
Medulloblastoma	Medulloblastoma.

COMMENT

While some authors,[34, 40, 44, 45] have tried to grade carcinoma with mathematical accuracy and have suggested methods of their estimation, such as "clinical index of malignancy,[45] and 'histological malignogram'[34] there are others who do not consider various qualifying factors for grading, but merely give a section a thorough going over and estimate the percentages of differentiated and de-differentiated cells[22]. Any consideration of this subject necessitates emphasis on certain facts. The method of grading malignant tumors of different organs of the body vary, and different qualifying factors are recommended and are found valuable. Unless such factors are taken into account, grading would certainly be a matter of guess work. There is little doubt that reliable information, in regard to the prognosis in a patient with a malignant tumor, is obtained by evaluation of the histologic structure of the tumor, although, for determining the ultimate prognosis, due consideration should be given to clinical factors as well. In the field of group prognosis and evaluation of therapy and to estimate the comparability of different series of cases of a given type of cancer, grading is most valuable[76]. The information grading offers to a surgeon is, in so far as it indicates, the potentiality of the malignant cells to spread beyond the primary site. For the radiobiologist, who is primarily interested in tumor biology, particularly the behaviour of these cells under radiation, there are several radiosensitivity tables compiled to meet his requirements,[10, 16, 55].

In a growing subject, such as this, any light obtained from a new method of approach is welcome. The recent work of Glucksmann and Spear[26] is illuminating and worthy of record. These authors maintain that biopsy of a tumor gives valuable information and, therefore, advocate a quantitative analysis of repeated biopsies taken during the course of treatment. This is, according to them, a good means of studying the tumor potentialities and the extent of the reaction to radiation. In a series of 150 cases of uterine carcinoma, the authors found that the prognosis based on histologic studies made within three weeks of the beginning of treatment was correct in about 80 per cent of cases. Similar results have been obtained by them in approximately 300 additional cases of tumors taken from various sites of the body.

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Do you know that ?

About 644 million persons are having *Ascaris lumbricoides* with them. China alone has 355 million persons having friendship with these worms ! ! ! (Quoted from Lancet,) 2: 1197, 1951.

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A New Control for Heart Disease Pains.

A cold spray that stops excruciating pains of heart disease is being further studied. The "cold" spray, principally ethyl chloride, has already been tried out clinically by Dr. Janet Travell, at Cornell University. Applied externally to the patient's exposed chest, the spray anesthetic freezes off "trigger areas" that initiate the darting currents of pain.

In coronary thrombosis, caused by blood clots that block off vital circulation to the heart, severe pain can paralyze the recuperative powers of the heart in the crucial moments after an attack has begun. As a result, physicians in many cases must treat for pain and shock before launching important life saving measures. The spray would avoid this. Public Health Service, Federal Security Agency, American Practitioner 2: 1084, 1951.

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"Blood pressure resentment is toward being bossed, while ulcer resentment is against the world in general for not letting the individual be more of a success." Donald A. Laird in the journal "Banking." Quoted from American Practitioner, 2: 1090, 1951.

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The Seat of Emotions

The digestive tract is a favourite system for expressing emotional tensions or anxiety. It used to be rather common to see numerous scars on the abdomens of adults. Now-a-days, if there is more than one the doctor sometimes raises his eyebrows and remains alert for evidences of emotional problems which are expressing themselves in physical fashion. It is a strange thing that people feel no embarrassment as long as they can keep their symptoms on a physical level. They have no objections to one operation after another, but facing the fact that their symptoms are due rather to unsolved problems in living is too painful. Anderson, M. Camilla, in "Saints, Sinners and Psychiatry," (Quoted from American Practitioner, 2: 9, 1951).

RADIOLOGICAL SIGNS IN RICKETS AND THEIR DIFFERENTIAL DIAGNOSIS †

J. N. Berry *

In rickets, the radiological changes occur later than the changes in the blood chemistry but they truly portray the histological changes occurring in the bones, and not uncommonly, the clinician has to depend upon them for diagnosis and, certainly, for following up the progress of the disease under treatment. In this paper, the radiological changes in rickets have been described and illustrated from cases seen in the Medical College Hospital, Nagpur during the last two years.

Radiological changes are fundamentally the same in all the three types of rickets, *i.e.*, infantile rickets, under 3 years; late rickets, after 3 to 4 years including adolescence and adult rickets or osteomalacia. We have not come across any case of fetal rickets as described by Maxwell and Snapper[9] in China.

Radiological signs in rickets can be classified under two headings :

1. Those at the cartilage-shaft junction.
2. Those in the shaft of the bones, in the cortex and spongiosa.

CHANGES AT THE CARTILAGE-SHAFT JUNCTION

In the epiphyseal plate or the provisional zone of calcification, there is profuse and irregular proliferation of cartilage cells without calcification. This proliferating mass of cells presses deeply into the metaphysis producing broadening and fuzziness of the metaphyseal end. This is the earliest radiological sign and may be the only one in mild cases. Cupping of the metaphysis is inconstant, is much better marked at the lower end of the ulna than the radius and is seldom present in the bones at the knee joint.

In place of the narrow linear epiphyseal plate and the epiphyseal cartilage separating the epiphyseal ossification centre and the shaft end, a broad zone of proliferating cartilage cells now separates the two. This distance between the shaft and the epiphysis is further increased if the metaphysis itself is not calcified, as in severe cases, and the bone shaft, as seen radiologically, seems short.

When healing starts, the first change is calcification in the epiphyseal plate or the provisional zone of calcification and, as a result, it re-appears radiologically. Later the metaphysis gets calcified so that the bone seems to grow in length rapidly. The newly formed metaphysis shows

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† Paper read at the Annual Conference of the Association of Physicians of India, at Hyderabad, in March 1952.

* From Medical College Hospital, Nagpur.

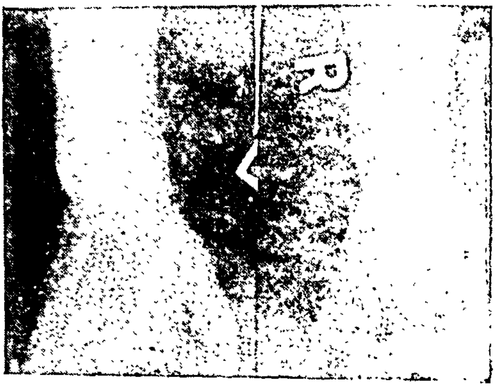

Fig. 1.—Infantile rickets S. K. 4 yrs. Note the enlargement, cupping and fuzziness of lower ends of radius and ulna. Thin cortex.

Fig. 2.—S. K. 2 mths. later, metaphysis calcified, increase in length of bony shaft, shaft thicker and denser.

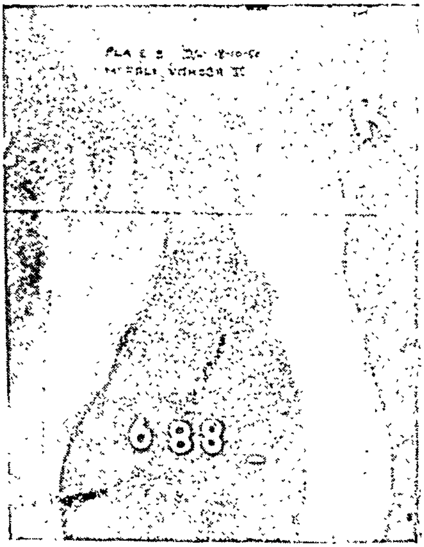

Fig. 3.—Infantile rickets, M. V. 2 1/2 yrs. Note the same features as Fig. 1, along with multiple fractures with bony callus formation. Note one "pseudofracture" at lower end of Rt. radius.

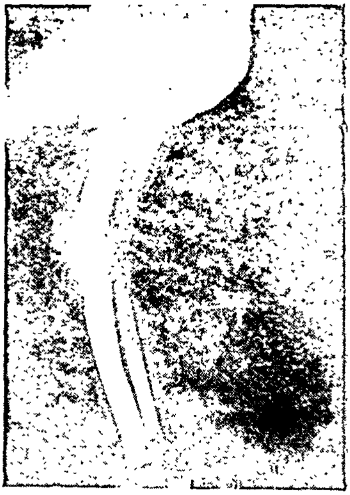

Fig. 4.—Congenital syphilis. M. A. 4 1/2 yrs. Note layers of fresh subperiosteal bone formation. No epiphysitis in this case. Mother and child's W. R. Positive.

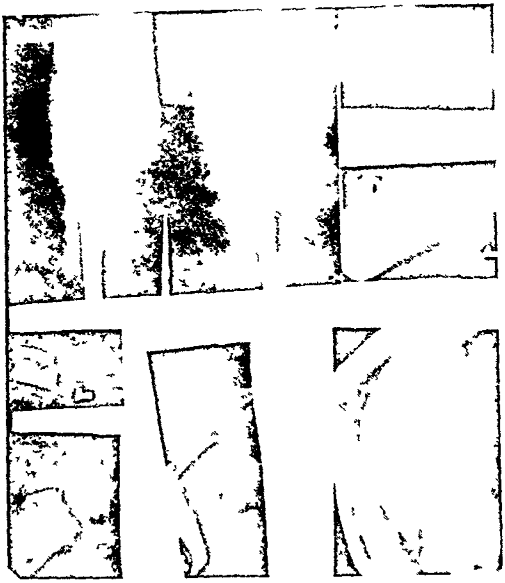

Fig. 5.—Scurvy. M. S. 1 1/4 yrs. F. Ch. Artificially fed, severe anemia and separation of the head of the Rt. humerus. Note thick, irregular epiphyseal plate with lateral spurring, zone of rarefaction behind it and partial fracture dislocation of epiphyseal plate through this zone (upper central-lower end of femur).

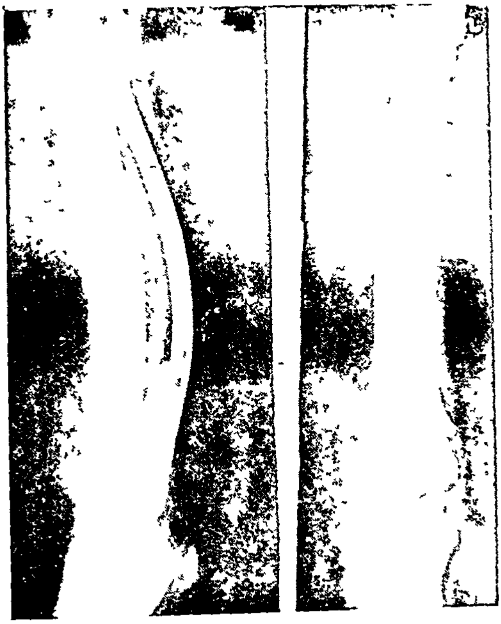

Fig. 6.—Osteogenesis imperfecta—Adult type. Miss N. 12 yrs. F. Ch. History of multiple fractures since birth. Blue sclerae, bones ,with increased tubulation.

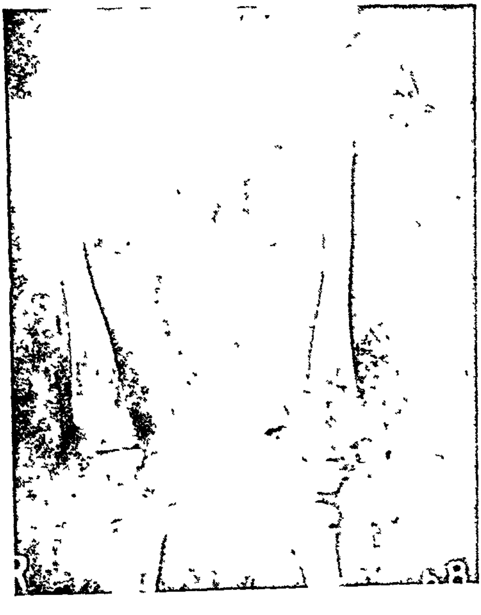

Fig. 7.—Renal osteodystrophy, P. G. R. 7 yrs. Ht. 31 1/2 inch. Wt. 26 lb. Genu Valgum. Albuminuria. Blood urea 76.6 mg. Note gross reticulation of lower ends of femora, absence of tubulation.

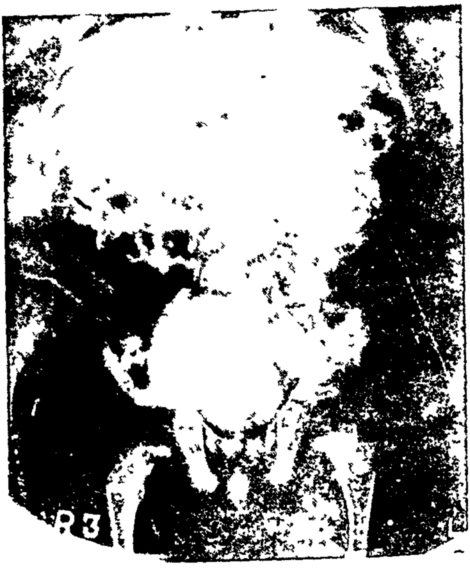

Fig. 8.—P. G. R.—I. V. pyelography—showing dilated ureters on both sides.

poor tubulation or remodelling. In the healed case, two or even more dense lines may be left at the epiphyseal end of the metaphysis, each representing calcification in a provisional rachitic zone or calcification in a relapse.

In late rickets the epiphyseal plates may remain uncalcified till long after puberty and the ossification may be delayed.

These changes at the cartilage-shaft junction are dependent on the growth of the bone and will be most marked at the growing ends of the bones in proportion to the velocity of growth at the particular metaphysis. According to Brailsford[2], these are present in the following order : Sternal ends of ribs, lower end of femur, upper end of humerus, lower end of ulna, lower end of radius and upper end of tibia. Hence they will be best marked in infantile rickets, less in late rickets and absent in adult rickets or osteomalacia when endochondral growth in length of the bone has stopped. These will be absent also when there is no growth occurring in infantile or late rickets due to concomitant undernutrition along with avitaminosis D as in extreme poverty and famine, or celiac disease and fibrocystic disease of the pancreas. Caffey[3] has called it hypoplastic or atrophic rickets.

CHANGES IN THE BONE SHAFT

These become evident a few weeks later than those at the cartilage-shaft junction and these will be the only changes in adult and atrophic types of rickets.

Bone formation consists essentially of two stages, *i.e.*, laying down a matrix called the osteoid tissue by osteoblasts and its calcification. In all types of rickets, this calcification suffers and the bone trabeculae are surrounded by broad seams of osteoid tissue or uncalcified bone matrix. As a result, the spongiosa appears more reticular than normal.

As the normal bone resorption and decalcification goes on unbalanced by fresh bone formation and calcification, the bones become decalcified, the cortex thinned, the spongiosa grossly reticular, the whole casting a shadow less dense than before.

This decalcification is less marked in infants and young children as their bone resorption is partly compensated by the formation of fetal fibre bone (Snapper[9]). Yet it may be extreme even in them.

Bending of the softened shaft or the rachitic metaphysis produces deformities like bending of the forearms and lower third of the tibia in infantile rickets, coxa vara and genu valgum in late rickets and triradiate pelvis in adult rickets, according to the site of stress at the particular age period.

During healing, the deformity gets fixed leaving a thickened cortex on the concave side of the bent bone.

Spontaneous fractures may occur and may be multiple. They are of the greenstick type in infantile rickets. When healing takes place, the callus formation is normal or excessive.

Besides fractures with bony callus formation, transverse ribbon-like zones of rarefaction, complete, or involving only the cortex on one side, may occur. They have been known as pseudofractures. Looser[5] called them *Umbauzonen* or zones of transformation. They are more marked in adult rickets than in infantile rickets. They are an important feature of Milkman's syndrome (Milkman[7], [8]). The presence of these Looser's zone in an otherwise grossly normal bone is characteristic of rickets (Albright and Reifenstein[1]).

DIFFERENTIAL DIAGNOSIS

Physiological cupping of the lower end of the ulna and radius when present may present some difficulty but absence of broadening and fuzziness of the metaphyseal ends and of changes in other bones like the sternal ends of ribs and the lower ends of the femora will distinguish the condition.

The epiphysitis of congenital syphilis seldom presents a problem. Apart from occurring in the first few weeks of life, only a part of the epiphysis is affected resulting in a mouse-bitten appearance. Often, periostitis and fresh subperiosteal bone formation is seen.

Growth lines at the end of bone, present in some healthy and chronically ill infants, may simulate healed rickets but the previous history and absence of other rachitic changes in the metaphysis and the shaft will distinguish the condition.

Lead lines, bismuth lines and phosphorus lines may present a similar picture but again the history of administration of bismuth for treatment of congenital syphilis or of phosphorised cod liver oil or in the case of lead, a history of exposure and its presence in urine and blood will clear any doubts.

Healing rickets may simulate a radiological picture of scurvy but here a dense irregular line—'*The Trummerfeld Zone*'—which is the calcified epiphyseal plate, projects laterally beyond the diaphysis with the formation of characteristic spurs and has a zone of rarefaction immediately behind it. Partial or complete separation of the epiphysis along with the brittle Trummerfeld zone which itself may be fractured may take place through the zone of rarefaction. Further, the bones show osteoporosis giving rise to a ground glass appearance. Marked density of the margin with rarefaction of the central spongiosa in the epiphyseal ossification centre is characteristic of scurvy. These changes also are best marked at the growing ends, knee, upper end of humerus *etc.* Subperiosteal hemorrh age may be present.

Multiple fractures when present in infantile rickets (Fig. 3) may raise the question of osteogenesis imperfecta but the bones are usually slender and show over-constriction and the shaft shows little cancellous tissue.

The thick bone type is chiefly confined to the prenatal variety of osteogenesis imperfecta and is limited to the first three months of life (Fairbanks[4]) and of course does not show the rachitic metaphyseal changes.

Radiologically, osteomalacia and late rickets may resemble hyperparathyroidism but can be distinguished by early and characteristic involvement of the skull and bones of the hands and by estimation of urinary calcium excretion and serum calcium phosphorus levels.

Postmenopausal osteoporosis, since it involves chiefly the vertebral column while the extremities are spared, should not cause any difficulty in differential diagnosis.

In renal osteodystrophy or renal rickets the bones present the same radiological picture as in late rickets but can be distinguished by blood chemistry, kidney function tests and pyelography.

SUMMARY

1. Radiological changes in the bones in infantile, late and adult types of rickets and their differential diagnosis have been described and illustrated by cases seen at Nagpur in the Medical College Hospital during the last two years.
2. Radiological changes are a replica of the histological changes in the bones and they occur both in the shaft and at the cartilage-shaft junction.
3. Changes at the growing metaphysis are its broadening fuzziness and cupping ; fading out of the epiphyseal plate and, in severe cases, non-calcification of the metaphysis. These are present only if growth is occurring at the bone end.
4. Changes in the shaft are rarefaction, reticulation of the spongiosa, deformities, fractures and pseudofractures.
5. Physiological cupping of lower ends of radius and ulna, growth lines, lead, phosphorus and bismuth lines, congenital syphilis, scurvy, osteogenesis imperfecta, hyperparathyroidism, postmenopausal osteoporosis and renal osteodystrophy have been discussed in the differential diagnosis and illustrated.
6. A case of infantile rickets with multiple fractures and pseudofractures and another of renal rickets are recorded.

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"... the 'modern trend' in medical practice—a trend which sets tradition on one side and reduces the doctor to the status of a stilted pseudo-scientist, intent on disease as such and on its discovery by clinical examination. tests and other laboratory aids, and forgetful that the patient is a sick man or woman, with his or her own frets and foibles, aversions and raptures ... The origin of the fault, for fault it is, probably lies in the early and incorrect use of the word 'case.' When the embryo doctor says that his case is doing well after operation, he will probably deny with some vigour that he is taking from the patient some of his human attributes ... but, unconsciously perhaps, he has identified the person with the disease and has set going a mechanism which may ..... help him to adopt what we have called the 'modern trend'." Quoted from Lancet, 2: 1200, 1951).

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Humbug

In a large city there were three eminent consultants of world wide reputation, one was said to be a good physician but no humbug, the second was no physician but a great humbug, the third was a great physician and a great humbug. The first achieved the greatest success, professional, and social, possibly not financial. Medical World. 75: Jan. 11, 1952.

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For Body and Mind

Rest in bed is in itself the cure of many maladies especially ailments of the fatigue group, minor heart troubles, and nervous disorders. Many patients take to it readily as retreat from the turmoil of the hour, but others protest against it and say: "Why should I not dress and lie on the sofa with a rug over me, which is just the same thing?" But it is not the same thing, for there is in rest in bed an abandon and sense of tranquillity which the best upholstered sofa cannot afford, and it gives overstrained organs like the heart, time to rally and recuperate. Medical World. 75: Jan. 11, 1952.

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The Moral Factor

In the fundamental clash between great nations when their existence is at stake the issue is determined by moral and not by intellectual factors. The part that character plays in medical diagnosis is not always appreciated. It is the quality which allows judgement to be exercised irrespective of worldly considerations which may snare the feet of the lighter breed of doctor. Medical World. 75: Jan. 11, 1952.

PLEURISY WITH EFFUSION *

Gurbuxsh Singh †

A GENERAL SURVEY

A general survey is always helpful in confirming the prevalent notions about any particular disease or in contradicting many features that have come to be accepted though without a basis of real scientific knowledge. This survey of 92 cases of pleurisy with effusion that is being presented, will not only confirm many a time-honoured aspect of this disease, but will also lead to some renewed scepticism about a few of its accepted features. Our text-books have so far given us the data observed in Western countries. It is thought necessary to obtain facts from amongst those who live in this part of the world.

INCIDENCE

During the year 1950, we had a total number of nearly 82,000 out-patients, and about 13,000 in-patients at the V. J. Hospital, Amritsar, of which, the cases of pleurisy with effusion numbered 139 and 229 respectively. The incidence amongst the out-patients works out to 0.25 per cent., and among the in-patients, 1.1 per cent. During 1951, however, the incidence was 0.45 per cent among the out-patients, and 0.6 per cent among the in-patients. The average for the two years together is 0.35 per cent of the out-patients, and 0.85 per cent among the in-patients.

Sex :—Amongst the 92 cases, the males predominated. The number of males was 56 and that of females 36.

Age:—The bulk of patients fell between the ages of 15 and 40 years, 68 out of 92 cases (73.9%). We had only 3 cases below the age of 15 years, of whom one was below 10 years and two between 10 and 15.

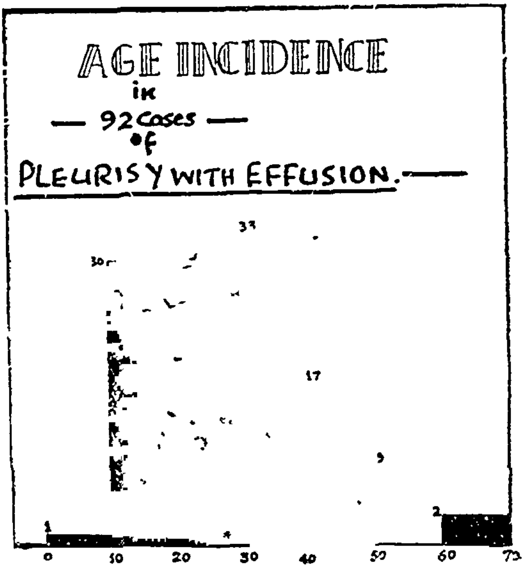

Fig. 1.—Showing the age incidence in 92 cases of Pleurisy with effusion.

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* Paper read before the Annual Conference of Association of Physicians of India at Hyderabad (Dn.), in March 1952.

† Professor of Clinical Medicine, Medical College, Amritsar and Visiting Physician, V. J. and Associated Hospitals, Amritsar.

Above 40 years, we had 11 cases,—9 between 41 and 50 and 2 between 61 and 70 years. Between 15 and 40 years the incidence according to decades was, 28 in the second decade, 33 in the third, and 17 in the fourth.

OCCUPATIONS

Except for 7 cases, in whose documents a mention of their occupations was wanting, the rest of the cases were classified into four categories :—

Class I, included people with outdoor occupations—like farmers, policemen and men of the armed services. Twenty-two per cent of the cases belonged to this group.

Class II, included semi-sedentary occupations—like hawkers, domestic servants, electricians, *etc.* Eleven per cent of cases belonged to this group.

Class III, included occupations of sedentary type—like clerks, shop-keepers, students, factory workers, *etc.* Twenty-three per cent. belonged to this group.

Class IV, included household work as the occupation. Thirty-seven per cent of the cases belonged to this group, and almost all of them were women.

FAMILY HISTORY

Seven patients gave a history of tubercular disease in the family, and one in the neighbourhood with active contact. Of these 8 cases, 5 were contacts of pulmonary tuberculosis ; 2 others had a family history of pleurisy with effusion, and the remaining one gave caries of the spine as a family history. Besides these 8 cases, 2 others gave a history of respiratory diseases in the family—(in the case of one, 5 sons and 2 daughters all died of some chest ailment)—and another 3 cases gave a family history of fever ending in death,—presumably tubercular.

PREVIOUS ILLNESS

The previous illness of the patients was considered in two categories :-

(1) Immediately preceding illness, which meant those illnesses which fell within one year prior to the onset of the present disease, and could be considered to have some possible relation with it. Twenty-seven cases gave such a past history. Of these the distribution was : dry pleurisy (4) probably concomitant dry pleurisy (3) ; pain in chest, probably dry pleurisy (8) ; pertussis (1) ; hemoptysis (1) ; cough (3) ; injury (1) ; and fever (6).

(2) Remote illness, which meant illnesses which occurred more than one year ago, and which may be considered probable relevant antecedents of the present illness. Eighteen cases advanced such a history. Of these the distribution was : pleurisy with effusion of the opposite

side (2) ; pneumonia, probably concomitant dry pleurisy (3) ; fever with pain in chest, probably dry pleurisy (6) ; pain in chest, probably dry pleurisy (1) ; chronic respiratory catarrh (1) ; enteric fevers (5).

SIDE AFFECTED

Forty cases had effusion on the left, 47 had right side affected. The affection was bilateral and simultaneous in 4 and bilateral alternative in one.

ENCYSTED OR FREE FLUID

Four cases showed encysted fluid, and the other 88, had free fluid.

SYMPTOMS

Mode of onset—85.8 per cent of cases had an insidious onset, and 14.2 per cent had an abrupt onset.

The symptom of fever was found in 75 cases, dry cough in 32, cough with expectoration in 23, pain in the chest in 42, pain in the abdomen in 12, pain in the back in 2, discomfort on breathing in 3, dyspnea on exertion in 28, dyspnea at rest in 6, orthopnea in 3, loss of weight in 11, loss of appetite in 8, gradual weakness in 6, night sweats in 4, headache in 2, a feeling of fluid in the chest in 1, hemoptysis in 1, abdominal distension in 3, palpitation in 2, tiredness in 2, constipation alone and alternating with diarrhea, vomiting, salivation, generalised edema, giddiness, and hoarseness of voice in one each. Hence, the most prominent symptoms in order of frequency have been, fever, pain in chest, back or abdomen, cough with or without expectoration, dyspnea, loss of weight, loss of appetite and gradually increasing weakness.

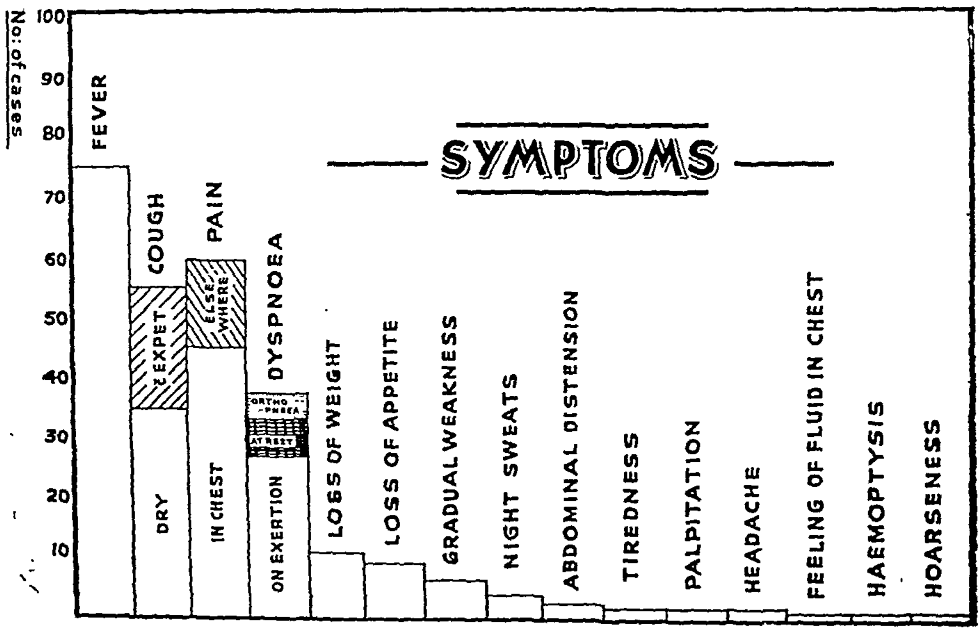

Fig. 2.—Distribution graph of 92 cases of pleurisy with effusion showing symptoms.

PHYSICAL FINDINGS

All cases showed clinical evidence of fluid in the chest except 2 cases, who showed no physical findings. These two were diagnosed on radiological examination, and in them the quantity of fluid was small. All the other cases were confirmed by radiological examination and almost all proved by paracentesis.

The following additional factors were found :—pleural thickening on the opposite side (3) ; an underlying lung lesion (11) ; a contralateral lung lesion (1), caries of the rib (1) ; pyorrhea alveolaris or caries of the teeth (5), infections of upper respiratory tract (2) ; and pericarditis with effusion (1).

LABORATORY TESTS

The leucocyte count was below 5000 per c.mm. in 7.9 per cent, between 5 and 10 thousand in 77.3 per cent, and above 10,000 (*i.e.*, leucocytosis) in 14.8 per cent.

Out of these, only 1.1 per cent showed lymphocytosis, eosinophilia, 2.2 per cent, and the remaining had an increase in polymorphonuclears.

Red Cells and Hemoglobin :—Considering that an average Indian is poor in total red cells and hemoglobin, as compared to the normal mentioned in text-books, those with a count below 4 millions, and with hemoglobin below 10 Gm. were classified as anemic. Red cells and hemoglobin were estimated in only 68 cases, out of which 39 showed a red count below 4 millions, and 20 had hemoglobin below 10 Gm., showing that anemia is a fairly common accompaniment.

Sedimentation Rate (*Westergren*) :—Taking into consideration that a fairly large number of female cases are included in this group, only 4 out of 75 showed a sedimentation rate of 11 to 20 mm. for the first hour, which may be considered to be within normal limits. The remaining were distributed as can be seen in the following table :—

Range in mm. for the first hour.	No. of cases.
21— 30 mm. for the first hour	4
31— 40 mm. do.	2
41— 50 mm. do.	8
51— 60 mm. do.	6
61— 70 mm. do.	9
71— 80 mm. do.	9
81— 90 mm. do.	7
91—100 mm. do.	13
101—110 mm. do.	5
111—120 mm do.	3
121—130 mm. do.	
131—140 mm. do.	
141—150 mm. do.	3

This brings out the fact that a raised sedimentation rate is one of the important laboratory findings met with in this disease.

Urine :—Urine showed no abnormality in any of the cases although textbooks mention that kidney disease is an importat cause of inflammation of the serous membranes. This is not borne out by this series of cases.

Serological Reactions Against Syphilis :—The Wasserman reaction was done in only 68 cases, and except for 2, who were ±, the others were negative.

Sputum or Gastric Lavage :—In 83 cases either the sputum or the gastric lavage was examined (when no sputum was produced by the patient). Only in 2 cases were acid fast bacilli found. In another case they were cultured from the sputum.

Pleural Fluid :—In 75 cases paracentesis was done and 41 cases showed a total protein quantity of 3 per cent or over ; 33 cases showed between 1.5 and 3 per cent ; and only one case, below 1.5 per cent.

Except for 9 cases, the globulin was positive in all, out of which 6 cases were markedly positive.

Microscopically, 7 cases showed high lymphocytic counts and 58 cases, low lymphocytic counts. By a high lymphocytic count I mean 25 cells per 4 mm. field or over ; and low lymphocytic count, less than 25 cells. Ten cases showed predominance of polymorphonuclear cells. Only in four cases were endothelial cells found. No case showed malignant cells. Smears revealed no micro-organisms in any case.

Out of these 75 cases, the pleural fluid was cultured only in 62. In the case of the others, either the reports are not available or not recorded. In 4 cases, *M. tuberculosis* were isolated from the pleural fluid by culture. In one case, *B. subtilis*, and in another case *B. fecalis alcaligensis* were reported to have been grown, probably contaminants. No growth of pyogenic organisms was obtained in any case.

TREATMENT

Whenever the fluid was found to cause dyspnea, or was up to the second rib, or was causing discomfort or showed no signs of resolution within 3 weeks, the fluid was removed as a therapeutic measure. Such cases numbered 27, and in six of these air replacement was carried out with the help of an artificial pneumothorax apparatus.

This work was started in 1948, when streptomycin, PAS, and the thiosemicarbazones were not available. Penicillin too, was not in a general supply at the hospitals and few patients could afford to buy it.

The first 22 cases were treated in 1948, and of these two were given the sulpha drugs and one was given penicillin. The others were treated on general lines only. The remaining cases were treated from 1949 up till now, and of these, 27 cases who could not afford any of the above-mentioned antibiotics, were treated on general lines alone. Treatment on general lines included rest, cod-liver oil, iron, pot. iodide and calcium. The other cases were put on to one or another or a combination of more than one antibiotics. Of these, 17 were given streptomycin only, 0.5 Gm. b.d. by intramuscular injections for 30-45 days. In one case, however, who had a strong family history of tuberculosis, the drug was administered for 82 days, and in another, who had polyserositis, it was given for 90 days.

Eleven cases were given streptomycin with PAS ; 2 were given streptomycin and thiosemicarbazone, 2 were given PAS alone ; and three cases thiosemicarbazone alone. Six cases had penicillin for 5 days (5 lac units per day), before streptomycin was instituted. Eight cases were given penicillin alone—5 lac units daily for 5—7 days.

RESULTS

Of those on penicillin alone, two were completely cured ; 3 were relieved and one did not improve. One left against medical advice. But in all those cases to whom streptomycin was given subsequently, penicillin did not do any good.

Of the 17 on streptomycin alone, 8 were cured completely; 2 relieved; one expired ; and the remaining 6 did not carry on the treatment and left midway against medical advice. The one who expired was an old man of 65 with an underlying disease of the lung—probably malignant. No laboratory evidence was obtainable, however, to prove the malignancy. He had been on streptomycin for 21 days when he died.

Of the 11 on streptomycin and PAS, 8 were completely cured, 2 relieved and one died. The one who expired was a young lady of 16, who did not react to treatment.

Of the 2 on streptomycin and thiosemicarbazone, one was cured and one left against medical advice.

Of the 2 on PAS alone, one was relieved and the other cured.

Of the 3 on thiosemicarbozone alone, 2 were cured and one relieved.

SUMMARY

A review of the problem of pleurisy with effusion is given as this is a fairly common ailment among those patients seeking admission at the V. J. Hospital, Amritsar.

The details regarding incidence, etiology, signs and symptoms are recorded, as well as the laboratory findings.

The treatment afforded these patients is outlined and the results are recorded.

THE GENERAL ADAPTATION SYNDROME

M. V. Rajapurkar, *

INTRODUCTION

It is difficult to review critically Selyes hypothesis of 'stress'. Yet any one who seriously wishes to follow the most important trend of medicine at the opening of the second half of the 20th century must try to understand Selye's gospel. Professor Hans Selye's concept of 'stress', and 'general adaptation syndrome', backed as it is by extensive scientific experiments, erudition, bold imagination, and comprehensive clear logic, is likely to revolutionise modern medicine. Its impact is already felt. How far reaching its effects will be, is too early to assess today.

THE HYPOTHESIS

Power to adapt to changing external conditions is an inherent quality of every living organism, otherwise, survival of the species would be impossible. In man, adaptation is specially important, exposed as he is to such diverse conditions as extremes of temperature and humidity, infections and trauma, mental and physical. The physiological mechanism that mediates the necessary changes to such stress and strain is hardly understood.

Claude Bernard showed how important it is to maintain the constancy of the 'milieu interne'. Cannon's concept of 'homoiostasis' and Frank Hartmann's "general tissue hormone" theory of the corticoids were abortive attempts to explain the mechanism, which interested Professor Selye. The curative action of fever, foreign proteins and other 'non specific therapeutic agents,' the 'Goldblatt clamp' for the production of experimental renal hypertension, and a host of other seemingly unrelated observations aroused the curiosity of Selye, who tried to integrate them into a single unified biologic system. Most of Selye's research has been devoted to 'the construction of bridges' as he put it, between these and many additional facts since he thought them to be interconnected in nature. To put it in Selye's own words "The key note of this unification was the tenet that all living organisms can respond to stress as such, and that in this respect the basic reaction pattern is always the same. irrespective of the agent used to produce stress. We called this response the general adaptation syndrome and its derailment the diseases of adaptation."

A NEW FACTOR IN THE ETIOLOGY OF DISEASE

The common causes of disease so far known are traditionally classified into the following groups :—

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1. Congenital and inherited abnormalities, (*e.g.*, hemophilia).
2. The effects of excess of a chemical agent, *e.g.*, lead poisoning.
3. The effects of deficiency, *e.g.*, deficiency diseases.
4. Infection or infestation by viruses, bacteria, fungi or animal parasites.
5. Physical trauma.

There exist a large number of diseases whose causation we do not comprehend or comprehend but dimly. Attempts to explain the etiology and to establish a cause-effect relationship have been constantly going on. According to Professor Pickering, in the present century, three hypotheses of disease have attempted to explain these maladies :

(*a*) *Focal Sepsis* :—This supposed that small localized infections could produce generalized disease, the remote manifestations being due to either bacterial disseminations, allergic tissue response, or absorption of toxins from the focus. This theory, once very popular, has lost most of its appeal for various reasons.

(*b*) *Psychosomatic Organs* :—The psychosomatic hypothesis attributes diseases to certain abnormal states of minds. It tries to explain such widely divergent diseases as ulcerative colitis, peptic ulcer and rheumatic diseases. Critical analysis of available evidence does not strongly substantiate this hypothesis.

(*c*) *Diseases of Adaptation* :—The theory of 'diseases of adaptation' as presented by Hans Selye of the University of Montreal is the last recruit to the series, which I propose to review briefly.

GENERAL ADAPTATION SYNDROME

Definition :—It is known that there are certain specific defence reactions, *e.g.*, formation of specific antibodies, adaptation to cold, habituation to drugs, hypertrophy of much used muscle groups, proliferation of the epidermis when exposed to pressure or friction. Selye thinks that besides these known physiological defence reactions, there are certain mechanisms which help to raise resistance to damage. According to him, the endocrines play an important part in these latter reactions, which occur irrespective of the specific nature of the damaging agent. The sum of all those non-specific systemic reactions of the body which ensue upon long continued exposure to stress has been termed the "general adaptation syndrome."

Stressor Agent :—The stressor agent may be very varied. Selye has studied the reaction of experimental animals to a variety of stresses, such as severe infection, poisoning, intense muscular exercise, exposure to cold, solar or reontgen irradiation, nervous stress, and fasting, and has described the systemic reactions. Stressor agents also include such agents as traumatic, surgical, obstetric, anaphylactic, emotional, electric and pleural shock. Effects of hemorrhage, anoxia, bacterial toxins, drugs such as alloxan, colchicine, formaldehyde, histamine, peptone, thiourea and turpentine have also been included as stressor agents.

Reaction :—According to Selye, each stressor agent evolves two distinct sets of reactions : First a non-specific defence measure (G.A.S.) which consistently follows a basic defence pattern, regardless of the nature of the stressor agent, and a second, more variable in character and specific to the nature of the damaging agent. The latter may to some extent influence the detail of the former. The skeleton of the 'general adaptation syndrome' may be presented as follows : Under the influence of the stressor agent the body adapts itself and the process evolves in three stages :

(*a*) The "alarm reaction."
(*b*) The stage of resistance and
(*c*) the stage of exhaustion

1. *The alarm reaction* has two phases, 'shock' and 'counter-shock. The stage of shock represents submission of the organism to the attack and is characterised by hypothermia, hypochloremia, hypotension, hemoconcentration, increased capillary permeability, depression of the nervous system, transient hyperglycemia changing to hypoglycemia, leucocytosis and gastrointestinal ulceration and enlargement of the adrenal cortex, increased corticotrophin and corticoid production. If the stress is of mild intensity the phenomenon of shock is followed by counter-shock where most of these features are reversed.

2. *The stage of resistance* :—This is essentially a "protracted counter shock". During this phase all the nonspecific systemic defence reactions are mobilized in response to that particular stress. Thus resistance to one form of stress is gained at the expense of resistance to other forms of stress.

3. *The stage of exhaustion* :—Should the stress persist or the onslaught prove very heavy, the stage of exhaustion ensues accompanied by decline of the defence reaction and even death. It should be noted that specific resistance to the agent with which the animal is treated decreases during the shock phase of the alarm reaction and increases during the countershock phase, reaching its maximum during the stage of resistance. No "crossed-resistance is established".

The term "adaptation energy" is used to describe the ability of the organism to acquire resistance to stress. Any agent capable of producing an alarm reaction is defined as an "alarming stimulus".

If the stress is powerful and progressively increasing, all the three stages may not be distinct. The succession of events may be very rapid and shock manifestations become powerful and intense culminating in death, as in an attack of malignant diphtheria. The stage of resistance morphologically is marked by thymicolymphoid involution and eosinopenia.

On the other hand, the effect of the stressor agent may be so mild that only transient hyperglycemia, tachycardia, and leucocytosis bear witness to the shock. Alarm reaction is not always a pathological phenomenon. It can be produced by mild exposure to stress, which is unavoidable in the course of every day life.

Only non specific damage and defence are integral parts of the 'general adaptation syndrome', but the specific actions of the stressor agents modify the course of the general adaptation syndrome (*e.g.*, the glycemic curve will deviate from the characteristic pattern if insulin is used as the stressor agent). In this sense they are called "conditioning factors". Certain factors, not connected with stress, also modify the pattern of the adaptation syndrome. Such factors are heredity, pre-existent disease of certain organ systems, and the diet.

DEFENCE

The mechanism of defence is co-ordinated through the hypothalamus and pituitary which are stimulated through a pathway as yet unknown. Selye suggests, "Probably, either humoral or nervous impulses, coming from the site of direct injury, can induce the 'hypothalamus-hypophysis' system to gear the body for defence. Subsequently, both of the two integrating mechanisms, the nervous and the endocrine systems, are alerted.

(*a*) *The Nervous Defence Mechanism* :—The part played by the nervous system is to some extent understood. It acts through the autonomic nerves to the peripheral organs. The stimulation of the adrenal medulla leads to the liberation of adrenaline and noradrenaline into the circulation, causing vaso-constriction and a hypertensive response. There is some evidence of a simultaneous cholinergic discharge during systemic stress. However, the predominant response, is a defensive vasoconstriction and hypertension.

The nervous system also participates in many other defensive reactions during the general adaptation syndrome, *e.g.*, the regulation of water metabolism through the posterior lobe, the blood sugar through the hepatic branch of the sympathetic division and the blood count through splenic contraction.

(*b*) *The Hormonal Defence* :—We are concerned, principally, with the less known workings of the hormonal defence. Besides producing shock, the stressor agent stimulates the pituitary producing the so called "shift in anterior lobe hormone production". There is an increased production of the adrenocorticotrophic hormone (ACTH) with a diminished production of the growth hormone, gonadotropic hormone and thyrotropic hormone, which are not essential during an emergency for preserving life. Increased production of ACTH leads to excessive secretion of the cortical hormone. According to Selye these are of two kinds (*a*) gluco-corticoids (G. C.) which control organic metabolism including that of protein and of carbohydrates and (*b*) mineralo-corticoids (M. C.) which control the electrolyte and fluid balance.

Gluco-corticoids :—ACTH is a gluco-corticotrophic hormone which stimulates the adrenal cortex to secrete gluco-corticoids-compound-F and cortisone.

The G. C. cause polymorphonuclear leucocytosis, lymphopenia, and eosinopenia. The thymo-lymphatic system undergoes lympholysis, there is increased phagocytosis and antibody formation and gluconeogenesis.

The gluco-corticoids generally inhibit excessive proliferation of fibrous tissue, the formation of intercellular protein deposits, (*e.g.*, hyalinosis, collagen disease, allergies) and excessive granulomatous defence reactions. They tend to lower the erythrocyte sedimentation rate through their effects upon blood proteins. In all these effects they are antagonists of the M.C.

The gluco-corticoids however, have slight mineralo-corticoid activity. In very heavy doses they can produce hyalinization and disintegration of the kidney glomeruli, thus acting like M. C. in this respect.

Mineralo-corticoids :—There is data to suggest that under conditions of stress the mineralo-corticoids are likewise increased. The M.C. share with the gluco-corticoids the ability to increase the general resistance of adrenalectomized animals. M.C. have two important actions: (*i*) Retention of sodium chloride, and water with elimination of potassium. (*ii*) When given for a long time they cause: distension of the convoluted tubules, proliferation of the spiral segment, hyalinization of the glomeruli, proteinuria, hyaline cast formation and eventually nephrosclerosis and development of the "endocrine kidney", due to gradual constriction of the glomerular capillary bed. M. C. also encourage formation of arteriosclerotic changes with a tendency to produce periarteritis nodosa, and hyalinosis with hypertension.

PITUITARY AND THE CORTICOIDS

Both types of corticoids act upon the anterior lobe and inhibit its ACTH production through the so called phenomenon of "compensatory atrophy."

Selye believes that these two main groups of cortical hormones are stimulated by two separate principles of the pituitary. Pure ACTH is predominantly gluco-corticotrophic.

Excess secretion of mineralo-corticoids can be stimulated by certain impure pituitary extracts such as 'lyophilized anterior pituitary tissue'

(L.A.P.). The action of L.A.P. is intensified by the simultaneous administration of ACTH. Selye suggests that this qualitative alteration of ACTH is probably due to some factors ("X") present in the impure pituitary extracts or L.A.P. This "X-factor," according to Selye, may be either one of the known pituitary principles or a principle which has so far not been isolated.

Furthermore, in response to stress, the pituitary itself discharges, predominantly gluco-corticotrophic or mineralo-corticotrophic principles.

DISEASES OF ADAPTATION

A person should be healthy if the system is efficient and hence the adaptation is perfect. Unfortunately, many factors disturb the basic pattern as described.

As already emphasized, the two groups or corticoids are mostly antagonists. Excessive production of one over the other (especially M.C.) is harmful and upsets the defence mechanism as indicated. Proteins, whether exogenous or endogenously liberated, augment M. C. action. Sodium renders the kidney sensitive to mineralc-corticoids. Topical chemical irritation augments the fibroplastic and hyalinosis producing action of mineralo-corticoids.

These in turn are influenced by heredity, species differences, previous exposure to stress, the nutritional state of the organism, *etc.* These, are termed by Selye as "conditioning factors". The specific action of individual stressors also acts as conditioning agents. It is these conditioning factors which considerably modify the basic patterns at various points. This makes it possible to include such widely divergent conditions as rheumatoid arthritis, diabetes, hypertension, to be included as 'diseases of adaptation', and to be ascribed to the same causative agent-systemic stress.

EXPERIMENTAL EVIDENCE

Selye has induced many of these diseases in experimental animals by administering desoxycortone acetate, a typical mineralo-corticoid.

Selye, Sylvester, Hall and Leblond' injected rats with comparatively high doses of desoxycortone and produced nephrosclerosis and high blood pressure. In addition to nephrosclerosis the most striking feature was the formation of "Aschoff bodies" in the heart and the presence of 'periarteritis nodosa'. The rarity of joint lesions was conspicuous. However, arthritis developed more regularly and with greater frequency in adrenalectomized and thyroidectomized rats. It was also shown that unilateral nephrectomy and sodium chloride treatment increased the sensitivity of rats to desoxycortone dosage. These may be acting as conditioning factors. The great clinical and histologic similarity of arthritis in experimental animals and men is striking.

Selye[5] reported the production of arthritis by local formalin injection. This "formalin arthritis" is aggravated by pre-treatment with desoxycortone and almost completely inhibited by cortisone or ACTH.

Selye[7] again reported that desoxycortisone (Reichstein's compound-S) a compound normally occurring in the adrenal cortex, was very effective in raising blood pressure and water turn over. It also caused wide spread and intense periarteritis nodosa, acute nephrosclerosis and granulomatous nodules in the heart, accompanied by organ changes similar to those which occur in certain so called "collagen diseases" of man. This, according to Selye, is further proof that naturally occurring corticoids may be involved in the pathogenesis of those "diseases of adaptation" which respond favourably to therapy with glucocorticoids or ACTH.

It is not possible to survey all the experimental work of Selye in the compass of this article. Evidence quoted however is fairly convincing. The diseases listed by Selye as "diseases of adaptation", are as follows :—

Diseases of Adaptation due to Endocrine Disturbances :

(A) **Hyperfunctional**

(*a*) Primary diseases of endocrines which participate in G.A.S.

1. Cushing's diseases.
2. Adrenal tumours with "Cushing's syndrome"
3. Chromaffinomas.
4. Coarctation of the renal artery and other primary diseases of the kidney conducive to hypertension.

(*b*) Secondary diseases due to excessive (or abnormal[1]) response of endocrines to stress.

1. Some types of hypertension.
2. Periarteritis nodosa (also arteriosclerosis and other vascular lesions).
3. Nephrosclerosis.
4. Some types of nephritis (?)
5. Rheumatic diseases (?)
6. Waterhouse Friedrichsen Syndrome.
7. Eclampsia (?)
8. Accidental thymus Involution
9. Some types of appendicitis (?)
10. Some types of tonsillitis (?)
11. Gouty arthritis (?)
12. Some types of diabetes.

(B) **Hypofunctional**

(*a*) Primary diseases of endocrines which participate in the G.A.S.

1. Simmond's disease (Pituitary hypofunction).

2. Addison's disease.

(*b*) Secondary diseases due to insufficient response of endocrines to stress :—

1. Secondary shock (relative hypocorticoidism).
2. Acute gastro-intestinal erosions (Curling's ulcer).

CRITICISM

Selye's list of diseases of adaptation is thus long and to use his own expression 'polymorphic'. Not unnaturally, it has met with a barrage of criticism, all of which cannot be surveyed here. Some of the attractive explanations as given by Selye are mentioned below :—

According to Selye, the principal reason for the polymorphism is the so called "conditioning factors", namely the specific effect of the stressor agent along with exogenous and endogenous factors which can effect certain pathways or target organs in G.A.S. He explains the specific action of the stressor from an example in chemistry saying that though all acids have many basic qualities in common, no two acids and no two stressors, are exactly alike. This he suggests is further modified by the extraneous and endogenous factors influencing the target organ — 'peripheral conditioning'. This has been compared to the electric current, which is always of the same quality and travels along the same pre-existing channels but can be used at the periphery for different purposes in different amounts by the interposition of different gadgets.

Perhaps the next most serious objection to the G.A.S. is that it has not been conclusively proved that desoxycortisone (D.C.A.) as such is secreted by the adrenal cortex. Most of the experimental work, however, is based on injection of D.C.A. Similarly, there is no proof that the "X-factor", referred to is secreted by the pituitary.

The doses of D.C.A. used in experiments is more than can be produced by the body. This objection has been met by the suggestion that under conditions of stress the body may be able to secrete much more than normally. Selye met this objection more convincingly when, later, he produced lesions in sensitized animals (unilateral nephrectomy and high sodium diet) with much smaller doses of D.C.A.

The objection that urinary excretion of corticoids is not always demonstrably increased in diseases of adaptation is sought to be explained on the basis of 'relative hypo-corticoidism' rather than absolute deficiency.

Simultaneously with the enunciation of Selye's hypothesis came the notable observations of Hench and Kendall, who showed that rheumatoid arthritis could be relieved by ACTH and cortisone. This did not very much support Selye's hypothesis. Selye reoriented his hypothesis by suggesting that it is not the indiscriminate stimulation by ACTH of the adrenal cortex as the selective stimulation of G.C.'s or M.C.'s. To support his contention Selye produced formalin arthritis in rats and showed that it is made worse by the injection of mineralo-corticoids or lyophilized pituitary extract. Cortisone or ACTH, however, prevented the arthritis.

Clinical Utility :—It is difficult at this stage to appreciate or imagine clearly a clinical application for G.A.S.

Selye believes that many of the time honoured non specific therapeutic measures, like fever therapy, protein shock, blood letting, *etc.*, act through the 'general adaptation syndrome,' principally by stimulating ACTH and gluco-corticoid production. If this is true we may be able to use ACTH and G.C.'s. in many diseases where non specific therapy was used, empirically. To put it in Selye's words, "we are on the threshold of developing a modern version of non specific therapy which is much more effective than the old and lends itself better to a scientific analysis of its mechanism".

In his experiments Selye has produced hypertension, nephrosclerosis *etc.*, and has shown that proteins and salts act as "conditioning factors". He therefore thinks that understanding of the G.A.S. shall help us to prescribe diets on a much more rational basis.

He further suggests that it shall help us to rationalize the use of ACTH and cortisone.

COMMENTS

Professor Han Selye's hypothesis is a very brilliant generalization which has the charm of synthesis and though not fully convincing is highly appealing and deserves a very close study.

Two very fundamental points emerge from this hypothesis. One is that one agent can produce a large number of diseases depending upon the conditioning factors which sensitize or desensitize the organ. The common belief that every disease must have its own separate cause seems to be discredited. The second fact brought forcefully to our notice is that—"upto now, medicine attempted to attack only the damaging pathogen– to kill germs, remove tumours, neutralize poisons, *etc.*" As regards defence, modern medicine knows little. Selye's hypothesis tries to explain the latter and opens entirely new channels for research and brings a new outlook to medicine.

Some people have referred to this concept as 'just gas'. That is probably unfair. To my mind it is the bible of a new medical religion. There is undoubtedly much that is yet only partly understood as Selye himself admits, "many lines in our sketch will have to be hesitant, some even in-correct, if we try to put on paper now what we still see only vaguely".

This brilliant hypothesis is a challenge to much conservative routine thinking in medicine and deserves a very close study. It may hold the seeds of a revolution that may change the face of modern medicine.

SUMMARY

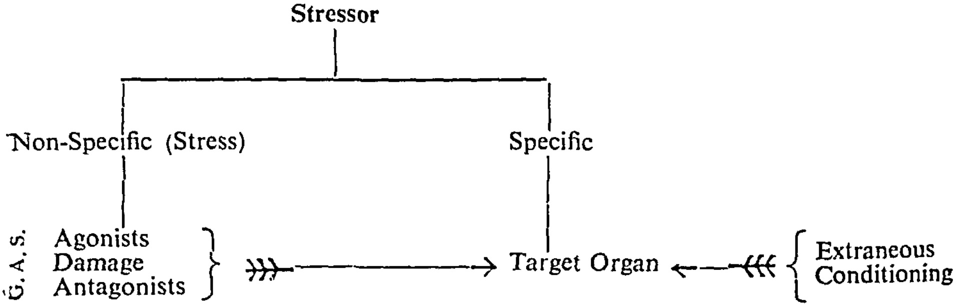
A large number of agents can act as 'stressors.' Any stressor agent has two effects. A specific effect peculiar to that particular agent and second non specific action through the general adaptation syndrome.

This causes defence and damage. The defence acts through a nervous and humoral mechanism, the former much better understood and the latter poorly known. Stress causes shift in the 'anterior lobe hormone production' leading to increased production of ACTH, probably aided by the "X"-factor which through the hypophysis-adrenal mechanism leads to selectively greater production of the mineralo-corticoids, which are the offending agents. Stress also causes some degree of damage through the G.A.S.

The agonists and antagonists, thus mobilized, act on the target organ and try to adjust it to the injury.

The final response of the 'target organ' is further conditioned by extraneous factors like heredity, diet *etc.* Ultimately the reaction of the target organ will be the resultant of : (*a*) the specific action of the stressor, (*b*) the effects of the resulting G.A.S. and (*c*) the extraneous conditioning factors.

The permutations and combinations can be so many that the multiplicity of the 'adaptation diseases' can be explained. This is best summarized in Selye's own diagram :—



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Occupational Health

Research on occupational health has continued to form a substantial part of the Council's programme and the new units set up in the immediate post-war period for the purpose of carrying out work in this field are now firmly established.

Minor Injuries and Skin Diseases.—The Industrial Medicine Research Unit in Birmingham, under the direction of Professor J. R. Squire, has continued its studies of two important causes of lost time in industry minor injuries and skin diseases. Improved methods of treating injuries which have been started in local factories have been shown to reduce lost time and more attention is now being given to measures of prevention.

This Unit has also continued to study the incidence of skin cancer among workers exposed to the cutting oils used in the engineering industry. This kind of skin cancer might be prevented altogether if industry could be supplied with non-carcinogenic oils for those processes involving skin contamination, but before such oils can be produced, fundamental research into the carcinogenic action of mineral oil is required.

Pneumoconiosis.—The largest single effort which the Council is making in the field of occupational health still remains the attack on pneumoconiosis in coal miners. It has been shown that two broad stages can be distinguished in this disease. The earlier stage of simple pneumoconiosis is thought to be due solely to the deposition of dust in the lungs and it seems likely that if exposure ceases before the condition is well established, the prospect both of a normal life and of being fit for other employment is good. In the later stage of "progressive massive fibrosis" the outlook is very different, and deterioration of health usually occurs with or without further exposure to dust. The view is gaining ground that this second stage, to which the condition largely owes its ill reputation, may be due to a tuberculous process occurring in a lung whose susceptibility and reactions have been altered by simple pneumoconiosis. The Council's Pneumoconiosis Research Unit in South Wales has therefore, in collaboration with the Welsh Regional Hospital Board and other local interests, launched an ambitious investigation into the relationship between tuberculous infectivity in the community and the development of progressive massive fibrosis in coal miners. This scheme, which is being carried out in the Little Rhondda Valley with the co-operation of its inhabitants involves regular X-ray examinations of the entire population and isolation or admission to hospital of all cases of tuberculosis liable to infect others. It is hoped that in this way the risk of tuberculous infection will be substantially reduced in the valley, and it should then be possible to observe whether progressive massive fibrosis continues to develop there among miners with simple pneumoconiosis. The scheme is, of course, a long-term one and the results cannot be expected for at least five years. Medical World. 75: Dec. 21, 1951.

A GENERAL THEORY OF HUMAN BEHAVIOR

M. G. Good †

In the last decade or so I have been engaged in extensive work on rheumatism. Since the cardinal symptom of that group of maladies is pain—leading secondarily to disturbances of movements and locomotion—and a purely subjective phenomenon, it appeared, from a strictly scientific point of view, of utmost significance to find objective criteria for patients' main complaint. The thorough investigation of hundreds of rheumatic sufferers, with this view in mind, led to the discovery that the painful areas as mapped out by the patients are of a referred character, and originate in muscular areas, which are anatomically defined and ascertainable by objective signs. These "myalgic spots" elicit on pressure, in addition to agonizing wincing pain, a reflex-like jerking in a part of the body, or make him "cut a face." This sign is absolutely reliable and practically pathognomonic. It was further established, in many hundreds of patients suffering from rheumatic myopathy (myalgia) or "fibrositis", that the injection of 1-2 cc. of novocain, provided it is done intramuscularly, accurately and thoroughly into each myalgic spot present, relieves the pain rapidly, and as a rule permanently, thus leading to a cure in a relatively short time.

It is common knowledge that rheumatic sufferers, especially if the malady is of a longer duration, show definite signs of a neurotic personality. After the modern method of the objective diagnosis of pain proved capable of enabling the physician to check a patient's complaint, I was greatly amazed to find that the former was not rarely unreliable, in so far as it became evident that some of the patients called any abnormal sensation "pain", which was not in accordance with the meaning of the term for the majority of individuals ; in other words the difference appeared to be a question of semantics. But what was even more amazing and perplexing are observations that patients suffering from an objectively ascertainable somatic (muscular) disease showed phenomena of resistance, transference, *etc.*, with which psychologists are so very familiar. These recurrent observations urgently requiring an explanation compelled the investigation of the question of motive or motives for so strange a behavior, and led up to the development of a theory of human behavior.

The theory I propose to put forward here is concerned with the axtreme importance of pleasure (satisfaction) for psychology and medicine. It appears pertinent to point out that "pleasure" is not meant in any derogatory sense, as in the popular expression "live only for pleasure". My definition of pleasure is free from any kind of value judgment and implies bodily as well mental (intellectual) contentment and the enjoyment we get by the satisfaction of our wants, needs, wishes and ideals. Pleasure may vary a great deal in quantity and quality ; it comprises the contentment from satisfying bodily needs—defecation, scratching, *etc.*—to the highest quality consisting in happiness from satisfied love, and the creative work of the scientist and artist. I have to call strong attention to the point that the theory is not concerned with the ancient philosophy of hedonism, which represented the doctrine that pleasure—bodily and mental (?)—is the main goal in the life of the individual.

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It is well known that Freud first introduced the "Lust and Unlust" principle into psychology, which he, however, later abandoned. The customary English translations are "lust" and "pain" which appear to the writer to be unsuitable for scientific purposes ; lust is a too emotionally colored word, whereas the term pain is an incomplete description. Displeasure is defined as the mental state of irritation, dissatisfaction and discontent, which arises when an individual is frustrated by being unable to satisfy his drives, needs, wishes and ideals. Displeasure varies quantitatively and qualitatively very much, from uneasiness, anxiety, anger, grief and worry to the wretched state of mind consisting of misery, disgust, distress and great suffering.

The theory of Human Behavior propounded here postulates that a certain quantity of pleasure (in the aforementioned sense) is indispensable for the maintenance of health, *i.e.*, for the proper functioning of the human body and mind. The theory implies that a deficiency of pleasure, *viz.*, if and when the quantity available to the individual falls below a certain minimum, leads of necessity to the impairment of bodily and mental health. The higher and highest degree of that deficiency may lead to severe illness and even death of the subject. It has to be noted that displeasure, unavoidably felt during the day by the individual, has to be taken into account ; displeasure has the reverse effect on the living body. In the daily balance-sheet of pleasure of a living organism, the amount of displeasure must, therefore, be entered on the debit side. For obvious reasons the quantity of pleasure required for health or optimal health cannot be estimated at present. No instrument—hedonometer—is available, which would make it possible to determine experimentally, at least quantitatively, the minimum of pleasure required for health.

On the other hand, there is no doubt that pleasure has a definite influence on the organism. It can be confirmed by the observation that it produces visible and invisible changes in the body. It leads to a dilatation of blood vessels, especially of the face and extremities, accompanied by a feeling of warmth in those parts. Pleasure improves and accelerates many functions of the organisms, *e. g.*, appetite, defecation, *etc.* ; under its influence the carriage is erect, the expression cheerful, the eyes lively. It is noteworthy that pleasure also gives rise to better and swifter cerebration, probably due to an improved blood circulation of the brain, and makes the individual take a livelier interest in his or her surroundings. Conversely, displeasure produces a slowing of bodily functions : diminished appetite, constipation, dry mouth, cold feet and hands, stooping shoulders, dull eyes, a drawn and often pale face (constriction of blood vessels), a worried look, slow cerebration, a low and often angry mood. A person suffering displeasure is less talkative, and little interested in his surroundings and fellow-creatures ; his capacity for work is diminished, the work itself inefficient and slow, as is also the taking of a decision. Negativism is often pronounced. In the higher degrees of displeasure, not rarely, aggressive and often emotionally colored reactions to every suggestion made by other persons to bring the victim out of his or her misery, are frequent. A fact well known to physicians is worth mentioning in this connection : displeasure and lack of pleasure often lead to somatic complaints, *e.g.*, sleeplessness, headache, pains in many parts of the body, *etc.* Depressed mood and other psychologic factors concerned with anxiety are known to be significant, eliciting causes of organic diseases, like angina pectoris, gastric ulcer, rheumatism including arthritis and others.

In view of the great importance of pleasure for the maintenance of health and well-being, it is not surprising that man is incessantly striving after pleasure, and is for ever most anxious to avoid displeasure. In parenthesis, it may be remarked that the same behavior can be noticed in intelligent animals, *e.g.*, dogs. The conscious or unconscious craving for pleasure during waking hours starts with the early morning cup of tea, if possible in bed, soon after awakening, and stops only, and perhaps not fully, during sleep.

The expectancy of pleasure or displeasure is, so it is claimed, the governing principle of human, and also of animal, behavior : every human activity is without exception, or with very few exceptions, due to or caused by a special motive (s) or reason (s). The same applies to any action suggested by others or oneself which is rejected or objected to, on the ground of rational or irrational reasons. According to the law of associations of ideas every activity connected with a pleasurable event or thought is libidinous. In the same way, mental associations with displeasurable events or thoughts cause an unpleasant feeling or annoyance. It may be noted that if there is a choice between two or more tasks to be accomplished, the individual is most likely to undertake the first or to prefer that which promises him a greater satisfaction. Similarly, if and when he is compelled by circumstances to do one of several things he dislikes, *i.e.*, which gives him displeasure, the individual is most likely to select that job which he dislikes least, or that which in his opinion or expectation offers him a chance of at least a little satisfaction, *e.g.*, by domineering or bullying—if he is so conditioned—, or the probability of an interesting chat with a person he likes, or similar motives.

Although the numerous activities of man differ very much individually in regard to the quantity and quality of pleasure or displeasure they give rise to, depending on upbringing, education, habits, moral standards, and generally speaking, on his mental make-up, I think it not inappropriate to give a short synopsis of the commonest sources of pleasure and displeasure.

A. COMMON SOURCES OF PLEASURE (HEDONICS)

. *Basic Needs.*

(1) Oral : food, drink, alcoholic and other beverages, smoking in persons addicted to them, sucking, licking, kissing.

(2) Anal : defecation, urination.

(3) Sexual : very important.

II. *Through the Sense Organs* :

(4) Visual : enjoyment of nature, works of art, moving pictures, seeing persons one likes or loves of the same, and more so, of the opposite sex ; watching sportive events, festive processions, ceremonies, receptions ; reading, watching plays, shows.

(5) Auditory : music, pleasant voice, interesting conversation, news being praised or flattered, wit, humour, jokes ; fun from ridiculing other people, especially one's opponents.

(6) Olfactory : pleasant smells (food, perfume, flowers, etc), least important.

(7) Gustatory : tasting of food, wine, flavors.

(8) Dermal : patting (caressing), tickling, scratching, warmth, touching soft materials.

III. *Secondary Pleasures* :

(9) Physical work : walking, sport activities, hunting, shooting, fishing ; fighting any professional or other work in which one takes a lively interest, especially if efficiently and successfully done, travelling.

(10) Games : cards, drafts, darts, chess and others.

(11) Acquiring money and other objects (so called possessive instinct).

(12) Love (excluding sexual) : narcicism, love of parents, relatives, friends, mankind, ideal objects, *e.g.*, truth, animals, *etc.*

(13) Satisfied ambitions : achievements in one's profession or occupation ; honors, academic and other degrees, titles, orders, *etc.*

(14) Anything conducing to heighten one's reputation, or increased self assertion and self-importance, *etc.*

(15) Intellectual activities : scientific, artistic and any other creative work ; inventions, exploration ; satisfaction from finding the relation between cause and effect (causality).

(16) Moral, ethical and esthetical pleasures : kindness, goodness, charity ; acquiring knowledge, work for the community, mankind, *etc.*

(17) Any need or desire satisfied, any activity in which one is interested, hobbies.

IV. *Amoral Activities* :

(18) Sadistic actions : annoying, nagging, bullying, domineering (very frequent).

(19) Lust of power : political and other forms of power (extremely frequent).

V. *Pathological (Sexual Perversions)* :

(20) Incest,
(21) Homosexuality (lesbism).
(22) Exhibitionism,
(23) Masochism and sadism,
(24) Fetishism.

B. COMMON SOURCES OF DISPLEASURE (ANTI-HEDONICS).

I. *Dissatisfied Basic Wants* :

(1) Oral : hunger, thirst, lack of alcoholic drinks and smoking (in persons addicted to them) ;

(2) Diminution of some excretory functions : defecation, urination ; dry mouth, mostly secondary.

(3) Sexual abstinence, relatively easily compensated by sublimation.
(4) Pain, suffering, ill-health in general,
(5) Fear and worries,
(6) Lack of security.

II. *Through Sense Organs* :

(7) Vision : seeing unpleasant objects or happenings ; seeing disliked or hated persons or objects.

(8) Auditory : noises, especially of unpleasant and sudden nature, *etc.*

(9) Olfactory : bad unpleasant, disgusting smells.

(10) Gustatory : disgusting, nauseating tastes and flavors.

(11) Dermal : touch of very hot or cold objects, cold hands or feet ; itching, paresthesias.

III. *Secondary* :

(*a*) of mental or mainly mental origin

(12) Mental overwork and fatigue, especially if not congenial to the individual's abilities.

(13) Frustrated love : in regard to sweetheart, parents, relatives, other people.

(14) Frustrated ambitions : also work unsuccessfully and inefficiently done.

(15) Being discriminated upon : in professional, occupational and other activities.

(16) Injustice suffered, unfair treatment.

(17) Boredom : a very frequent source of displeasure.

(18) Lack of chance or facilities to perform a task that the individual feels or imagines himself to be specially fit for.

(19) Inferiority feeling.

(20) Sense of guilt.

(21) Unsolved urgent problems.

(22) Taking a decision between two or more alternatives.

(23) Dislike of authority.

(24) Lowering of prestige and self-importance.

(25) Unhappiness domestic or from other sources.

(26) Being dominated : especially by an unsympathetic, disliked or hated person.

(27) Being bullied, tyrannized, *etc.*

(*b*) of other origin :

(28) Physical work: fatigue from exhausting or too prolonged work ; professional, occupational and other work in which the individual is totally disinterested.

(29) Bodily discomfort (excluding illness): long standing, queueing, *etc.*

(30) Extremes of heat or cold.

(31) Losses : of property, limbs, by death ; of fame or reputation.

(32) Interruption in work, talk, *etc.*

(33) Monotony: monotonous work, routine work without incentive.

(34) Losing fight, game, *etc.*

(35) Persecution and oppression ; being tortured.

(36) Being kept waiting unnecessarily.

(37) Danger to life, health.

(38) Troubles in up-bringing of children.

(39) Not able to keep up appearances.

(40) Any want, need or desire not satisfied.

It was mentioned above that both pleasure and displeasure produce many somatic and mental changes in the living organism. It is worth stressing that the changes may be brought about within a remarkably short time, as evidenced by the following observation which is very common indeed.

Mr. X, a middle-aged manager. On the morning of a cold muggy and rainy day in his office he was in a low and depressed mood ; the previous night his sleep was rather poor. He read the morning paper reporting a downwards trend in his line of business, and the business correspondence, full of annoying news still aggravated his bad mood. He felt utterly tired, depressed and unable to make any decision about many matters requiring his immediate attention. Sitting in the chair by his desk, utterly bored and listless, he reread almost mechanically the morning paper from top to bottom, but, the next moment he forgot what he had just read. He longed to go to sleep, if it were possible, in order to escape his miserable mood.

All of a sudden the phone rings, he lifts the receiver and hears the familiar sweet voice of the girl friend of his youth, announcing her unexpected return from abroad, and her intention of coming up to town in the afternoon. The news rejoiced him, and a stream of happiness seemed to flow through his whole body. He now looks a different man ; smiling pinkish face, bright eyes, erect carriage, and feels full of energy and beams. Within a few minutes he personally makes all the arrangements for the reception and entertainment of the visitor. He calls in his staff, easily takes the necessary decisions, gives the orders and dictates to his typist, without the slightest hesitation, replies to his correspondence ; he arrives in time at the air port to greet his friend on her arrival.

Such rapid changes brought about by purely mental happenings show conclusively the enormous influence and power of the mind on and over the body. How are these somatic changes to be explained ? Since the neuro-hormonal transmission of nervous impulses has now become a certainty it appears reasonable to make a similar mechanism responsible for the effects of pleasure on the organism. I, therefore, put forward the hypothesis that pleasure, of whatever source it may be derived, leads to the production and secretion into the body of a specific substance, which may be called the L-factor (L for libido), has the properties of a hormone, and is responsible for the effects of pleasure on the body and mind. Similarly, displeasure gives rise to the production of an AL (anti-libido) hormone of reverse somatic and psychologic effects. The question whether the L and AL substances are capable of neutralizing each other must at present be left open.

IMPORTANCE OF THE THEORY

It is only natural to ask what are the advantages gained by these conceptions to justify the advancement of a new psychologic theory. It is, therefore, incumbent on me to show that it is capable of fitting in and accounting for the observations under normal and morbid conditions. Introspection as well as observation of other people shows that expectancy of pleasure or displeasure is responsible for most human activities, possibly for every activity. Popularly expressed, the decisive factor of every action is "interest". If a person is interested in something, it means that he or she likes it, *i.e.*, the realisation of which would give him or her more or less satisfaction. The fact is often expressed in the popular saying, *e.g.*, to converse with him is a (source of) pleasure ; he takes pleasure in contradicting, likes to find mistakes (raising of one's self-importance!) ; or children love to ape their elders. The quantity and quality of pleasure derived from a special action seems to be conditioned by the personal "value" which the individual attaches consciously or unconsciously to it. I should like to quote in this connection a few passages from a novel by Stefan Zweig,[3] who was very much interested in psychology : "every task accomplished makes one happy"; "vanity is, after all, one of the most powerful driving forces, and weak natures in particular succumb to the temptation to do some things which, viewed superficially, makes them appear strong, courageous and resolute." A person (lieutenant) who felt very lonely because nobody took an interest in him says in the novel : "ever since I had first allowed this capacity for sympathy (sc. for a crippled young and pretty girl) to enter into my being, it seemed to me as though a toxin had found its way into my blood and had made it run warmer, redder, faster, pulsate and throb more vigorously"; "as soon as I discovered that my ability to feel pity was a force that not only stirred me myself positively and pleasurably, but extended its beneficient influence beyond my own personality, a strange metamorphosis began to take place within me."

There is no doubt that every task performed in accordance with the individual's professional, moral and ideal standards is pleasurable ; the reverse leads to great discomfort and displeasure. We unconsciously shirk or at least postpone as long as possible every task in which we are not interested, more so, if it is likely to cause us displeasure. But shirking our duty is, in the end, also displeasurable, because a sense of guilt often overwhelms us later. Events, desires and ideas which are highly emotionally colored, *i.e.*, the realisation of which will give us the greatest satisfaction, are mostly explained (by the person concerned) by irrational motives. And no amount of rational reasoning and discussion is able to convince the person of the fallacy of his arguments : "for most men in most matters, whether it be the justice of war, the rightness of a political creed (in which he is very much interested, M.G.G.), *etc.*, certitude in the entire absence of adequate evidence is easily arrived at and passionately welcomed" (Sullivan[2]).

TESTING OF THE THEORY

For years I have been submitting the theory to an extensive test, in analysing all the persons I had dealings with, in regard to the motive or motives of each of their actions and/or their omissions, especially when the behavior was not self-evident. In putting the question of motive to every case of action or refused action, which appeared unexpected or puzzling, I was enabled to find out the main springs of action of the individual concerned. In persons hitherto unknown to me, the analysis of the most likely motives of several or many of their activities and endeavors led in a short time to mostly one predominant motive, as a clue to their actions. Very often, this main spring of action could be confirmed by several spontaneous utterances of the subject, as well by the fact that his behavior under certain conditions could be predicted.

To my greatest surprise the observations led to the conclusion that the Adlerian concept of inferiority and its overcompensation to greater self-assertion, and will of power, appeared a rather frequent motive which best accounted for unexpected behavior in a great percentage of individuals. This motive seems, according to my observations, to play a predominant role in the relations between husband and wife, between parents and children, master and servant. The motive is often decisive for some activities of public servants, and even of some editors of scientific journals.

APPLICATION OF THEORY TO PSYCHOPATHOLOGY

I shall now turn to human behavior under pathologic conditions. It is my object to show that the theory is capable of explaining and accounting for some achievements of modern psycho-analysis. Freud has introduced into psychology the fundamental concepts of unconscious, repression, transference and fixation. To some psychologists, the term "unconscious" seems to imply a special region of the brain, which contains the forces collectively described as memory, instincts, habits, *etc.*, not directly known to the conscious mind, which is often in conflict with the latter, and thus may lead to neurosis and other mental disturbances. The conscious mind is that which feels, reasons and functions in the present. It is generally agreed that the working of the conscious depends to a very large extent on memory. The latter is customarily conceived as actuated by "traces", produced in the ganglion cells of the brain by former perceptions or other forms of stimulation. The changes brought about in these countless cells is thought, by some, to be due to a molecular motion caused by nerve stimuli and associated in our consciousness with the perceptions, objects and thoughts which originated them. We must remember that, the same molecular changes are produced by fibres—association paths—arising from or originating in stimuli conducted along special cells, which in their turn were stimulated by sense perception, their traces or other preceding associations. I personally believe that electrical changes due to Na°, K°, $Ca^{\circ\circ}$ and other ions, brought about by stimulation of ganglion cells forming the essence of the traces, is a more promising hypothesis than that of molecular changes.

But whatever the changes leading to the memory "traces" might be, memory cannot be accounted for without the assumption of such changes, and stimuli travelling along nerve fibers from other nerve cells. Viewed in this light, the unconscious can be defined as the sum of all the brain cells, containing memory traces, which cannot be revived—stimulated—at present, by reason of blockage of their association paths. The blocking may be due to disuse, *i.e.*, the memories have not been revived during many years (childhood impressions, formerly acquired knowledge, *etc.*, or to the fact that we have blocked the paths because of the displeasure connected with their remembrance. There is no necessity to postulate a special zone of the brain (cortex) containing the traces which cannot be stimulated at present. It is perhaps likelier that they are scattered among the ganglion cells of the conscious, *i.e.*, the traces of which can at present not be revived. Clinical neurology has provided evidence that the frontal lobes are the centers representing our intellectual abilities : thinking, feeling, moral and social conduct, appreciation of our sensations, *etc.* Whether the remaining, at present, unmapped regions of the brain, *viz.*, temporal, parietal lobes and insula are connected with intelligence, as originally assumed by Flechsig, is unknown. That under special favorable conditions the memories of "unconscious" cells can be revived and brought into consciousness, *e.g.*, by deblocking their association paths, either by using stronger stimuli or opening new paths, is not very surprising. It is a common daily experience that we, sometimes, cannot remember a name, object, *etc.*, which, a few hours later, spontaneously and without any apparent reason or voluntary effort, enters consciousness. The question as to how the blocked cells of the unconscious manage to influence the conscious and thus our conduct will be dealt with later.

The concept of repression can be discussed in a few sentences. In the light of the new theory, it obviously designates the voluntary and involuntary blocking of association paths which connect our conscious mental activities with the cells containing the traces of events and impressions the remembrance of which would give us more or less displeasure and suffering. It is, in fact, common experience that we very often dislike to remember unpleasant and unhappy experiences, and we often succeed in "forgetting" them.

A concept playing a very great role too, in psychoanalysis, is transference. It is the result of associations connected with and produced by the analyst with persons, events or actions liked (loved) or disliked (hated) by the analysed. These associations, elicited by the analyst, are therefore pleasant or unpleasant respectively to the patient. It is reasonable to assume that under positive transference, the patient "loving" the analyst, because receiving pleasure through him, is open to his suggestions and prepared to accept and comply with his advice. Under negative transference—displeasure through the analyst—the patient, on the contrary, takes up a negativistic attitude "resistance", and resists every endeavor to deal with his most significant problems urgently requiring a solution.

The mechanism of "fixation" describes the fact that a person is thwarted in his relations with the opposite sex, which normally would satisfy his sexual desires and give him great satisfaction and happiness. His sexual and erotic wants are concentrated on a person whom he cannot marry, or have any erotic relations with, by reason of the accepted moral and social standards prevailing in the society he happens to live in.

In the theory and technique of psychoanalysis interpretation of dreams is of fundamental importance. Their precondition is sleep. Now it has been confirmed experimentally that sleep usually varies very much in depth. During deep sleep the cerebral hemispheres do not, it would appear, function at all. According to Pavlov, sleep is characterized by the wide-spread inhibition of the brain. Probably, dreaming takes place during superficial sleep, when the inhibition of nervous activities is less pronounced : logical thinking and reasoning is not possible. But if we are able to dream, a number of ganglion cells and some of their association fibers must of necessity be disinhibited. It would appear not surprising that the brain cells selectively functioning during superficial sleep are those which deal with desires or instinctive needs of the utmost significance and urgency for, and consequently of the greatest interest to us, in other words promising great satisfaction if fulfilled ; or probably those cells storing the traces of sensations which have impressed the dreamer very deeply during the day (day remnants). In accordance with our theory of behavior, Freud claims that every dream represents a wish-fulfillment or an attempt at wish-fulfillment. In my opinion this has to be taken with a grain of salt : there are some dreams which are not in agreement with Freud's postulate. But for the greater majority, if not the vast majority of dreams, this concept forms the simplest and most reasonable explanation.

Freud's concept of censor as the controller of the contents of dreams is only another name for the dreamer's moral, social and other inhibitions, which are working to avoid displeasure accruing to the dreamer by the contents of the dream. But in order to get at least some of the pleasure he is craving for, the dreamer makes use of symbols. He dreams of persons, objects, perceptions and ideas which owing to his individual and personal associations are connected with the source of his enjoyment. Even in his dreams he cannot see or think of the object of his pleasure directly, because of the displeasure simultaneously associated with it, *e.g.*, by a sense of guilt, by reason of the fact that the enjoyment would be against his moral and social code (moral inhibition). To mention an example ; a mother fixated man dreams of sexual and/or erotic relations with a girl whom he happens to know, or to have seen lately, and who resembles his mother imago in as many respects as possible. He may dream of a female greatly resembling his mother, but showing a combination of features and traits taken from several persons he knows, who have impressed him during waking hours.

That some dreams, as many psychoanalyst claim, are intended to solve a problem confronting the dreamer is in full agreement with the theory 'every task accomplished makes one happy' (Zweig[3]). Even if a dream contains apparent or undeniable unfavorable events and impressions, *e.g.*, misfortune or death of a near relative, it may still be pleasant to the dreamer as a wish fulfillment. The same applies to a dream of self-punishment, because of its relieving effect on the dreamers sense of guilt. Similarly, the concepts of Jung regarding the causes of neurosis is in conformity with the theory. It is probably true that in some neurotics, especially in older people, sex in its narrow sense does no longer play a significant role. This is not in contradiction with Freud's teaching, if we remember his definition of sex in the wider sense. It is also possible or even not unlikely that some dreams in some neurotics could be or have to be interpreted as an indication of the dreamers proper conduct, *viz.*, the attempt to bring his conduct in line with his moral and social code, in order to get rid of his sense of guilt—great source of displeasure, perhaps also to get rid of the distressing idea of being of no use to anybody.

It would appear that the Theory of Human Behavior advanced here, *viz.*, that the conscious and unconscious, so to speak automatic striving of man after pleasure (satisfaction of his wants, needs and desires), and avoiding of displeasure, as far as possible, is the governing principle under normal and pathologic conditions. is capable of accounting in a simple way for the working of the mind. It shows that the modern schools of psychology and psycho-analysis do not differ from each other fundamentally. Although differing to a certain extent in technique and guiding concepts, they are in full agreement with the postulates of the theory. It is, therefore, not surprising that the three schools have been claiming good therapeutic results in a great percentage of their patients.

In conclusion it may be stressed that the theory makes use of one principle only. It does not require the assumption of many instincts, apart from the instincts of satisfying the most basic needs of food, drink and sex, which are obviously inborn capabilities. Other so called instincts, *e.g.*, gregariousness, *etc.*, are more likely to be due to experiences gained during early life valued and appreciated because of the satisfaction to the individual they give rise to. The theory accounts for the abnormal and amoral tendencies of some individuals: sexual perversions —homosexuality, lesbism, exhibitionism, fetishism—and other immoral activities like sadism, domineering, lust of power, which are indulged in because the persons concerned are not able to gain the minimum of pleasure required, in a way approved of by the society's moral and social code, or possibly that activity is to them a source of greatest satisfaction. It is to be expected that the theory may prove useful for the understanding of patients suffering from more serious psychic disorders like psychoses.

SUMMARY

Pleasure is defined as bodily and mental (intellectual) contentment and the enjoyment we get from the satisfaction of our wants, needs, wishes and ideals. The theory is advanced that a minimum of pleasure in relation to the displeasure unavoidably suffered by the individual is an absolute necessity for the maintenance of bodily and mental health. A deficiency of pleasure or a superabundance of displeasure may lead to serious and severe somatic as well as psychic disorders.

Pleasure and displeasure produce many visible and invisible, somatic and psychic changes, which are accounted for by the hypothesis that they lead to the production and secretion into the body of specific hormone-like substances L (libido) factor and AL (anti-libido) factor respectively. It is claimed that human activities are governed by the expectancy of pleasure, and the avoidance of displeasure, as far as possible. It is claimed that the theory fulfils the requirements of a scientific theory, *viz.*, in being capable of accounting for human behavior under normal and pathologic (neurotic) conditions. The theory appears to be in agreement with the fundamental concepts of psycho-analysis, and the main postulates of Freud, Adler and Jung.

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Specialists

A young medical man who runs off into a speciality, honestly believing that a human organ can be studied and treated separately, like the wheel of a watch, has not intellect enough to be a physician, and ought to have been discouraged from entering the ranks. He who undertakes it from mercenary motives ought to be frowned down, and told that his tendencies and faculties belong to the places where they sell their wares and souls for lucre, and call it business, not a sacred vocation. Medical World. 75: Jan., 4, 1952.

CURRENT MEDICAL LITERATURE

MEDICINE

TREATMENT OF RHEUMATOID ARTHRITIS WITH NITROGEN MUSTARD, Jimènez Dias, C., Lopèz Garcia, E., Merchante, A., and Perianes, J. : J.A.M.A. **147** : 1418-1419, 1951. 5 references.

The authors believed that treatment of rheumatoid arthritis with nitrogen mustard might be useful because a certain relationship seemed to be present between this substance and cortisone and corticotrophin. In the treatment of Hodgkin's disease with nitrogen mustard there is a progressive decrease in the lymphocytes and eosinophils as is also seen with the use of ACTH and cortisone. Chanutin and Ludewig have demonstrated that the suprarenal cortex undergoes a hyperplasia when acted upon by vesicating substances and Karnofske and his colleagues have reproduced symptoms similar to the "alarm" syndrome when they used nitrogen mustard. The authors first treated two cases of rheumatoid arthritis. Both were chronic cases and had been treated with chrysotherapy and the association of desoxycorticosterone acetate and ascorbic acid, with negative results. One patient had been suffering for 11 years and was bedridden with extremely painful swelling of the knees, ankles and finger joints. With the second injection of nitrogen mustard (6 mg.) there was the most astonishing result. The patient's condition was rendered almost painless the swelling reduced considerably and she could move her limbs and walk. With the fourth injection she was completely free from symptoms except for a slight ache, and could walk with ease. When seen a month later her condition was still satisfactory. The second patient, too, became completely free from pain, and all movements were recovered except where bony ankylosis was already present. The results were still evident two months after treatment was stopped.

Seven more patients with rheumatoid arthritis were subsequently treated with complete disappearance of pain and exudative phenomena and complete recovery of movement except where bony ankylosis was already present. The effect on rheumatism with nitrogen mustard parallels that on the blood cell count ; the fall in eosinophils from an initial 100-200 to values of 20-50 is usual after approximately the third injection and is even greater where the drugs effect is more intense.

Inspired by certain similarities the authors used nitrogen mustard in cases of prolonged status asthmaticus with great improvement after the first injection and complete relief after the second.

EUSTACE J. DE SOUZA.

HEADACHE: PRACTICAL CONSIDERATIONS, Friedman, A. P., and Von Storch, T. J. C.: Amer. Pract., **2** : 855-857, 1951.

The authors present their observations concerning headache, based upon ten years' experience in three clinics, devoted exclusively or predominantly to the study and treatment of headache. The most common types met with were migraine, tension headache and post-traumatic headache, others included tumors, aneurysms, sinusitis and other painful disorders.

For the evaluation of the headache problem they divide it into three categories : I. History ; II Examination, including laboratory tests, III Therapy.

1. *History* :—The patient should be allowed to describe freely his symptoms and related factors. The following information is important and should be elicited :—

(1) Onset and circumstances of onset. (2) The time of day most favourable to the headache. (3) The character of the pain. (4) Location of the pain. (5) Severity, duration and frequency. (6) Effect of posture and motion. (7) Associated signs and symptoms.

II. *Examination* :—This should always include inspection, palpation, percussion, and often auscultation of the head, if only to establish rapport with the patient. A complete neurological examination with special emphasis on the ophthalmological examination is indicated, as well as a search for sinus tenderness, observation of the nasal sinuses and an evaluation of cervical motility and sensitivity.

Laboratory procedures include urinalysis, complete blood count, serology, roentgenography of the head and neck, electroencephalography and ophthalmologic evaluation. Only the roentgenography and ophthalmologic examination have been occasionally of value.

Allergic studies, ear, nose and throat examinations, metabolic evaluations and examination of the spinal fluid have been of little value in the average case. Only an occasional headache was proved to be allergic ; surprisingly few chronic headaches could be attributed to disorders of the eyes or sinuses.

The most helpful procedure is a careful personality study. This is in reality a diagnostic as well as a therapeutic measure, but caution must be exercised as personality problems may not necessarily be the sole or even the predominant cause of headache.

III *Therapy* :—Headache is a symptom and not a disease. Headaches which are secondary to a specific acute illness are usually relieved by treatment of the primary disorder.

Migraine, post traumatic and tension headaches require a dual approach (pharmacopy plus psychotherapy). Failure is usually due to common errors in treatment, the most important of which are, (1) incorrect differential diagnosis, (2) failure to give medication early enough in any given attack, (3) inadequate dosage, (4) multiple etiology, (5) residual muscle spasm following a headache and (6) additional emotional stress.

For therapeutic success, the following is often necessary. (1) Dual psychological and medical approach, (2) utilisation of patient-doctor relationship to encourage the patient to ventilate and verbalise his emotional tensions, (3) manipulation of the environment, and (4) use of specific symptomatic medication to control attacks and thus reduce anxiety.

In migraine, symptomatic treatment is best obtained by parenteral administration of ergotamine (gynergen) or dihydroergotamine tartrate (DHE 45) and the oral use of a compound of ergotamine and caffeine (cafergot). The prevention of the attack is best accomplished by psychotherapy.

CHARLOTTE DE QUADROS.

SURGERY

MANAGEMENT OF OCCLUSIVE ARTERIAL DISEASES OF THE EXTREMITIES, LeFevre, F. : J.AM.A. **147** : 1401-1404, 1951. 20 references.

Arteriosclerosis and thromboangitis obliterans are the two most important occlusive peripheral vascular diseases. Basic principles that have been recognised many years ago are : (1) avoidance of trauma, (2) avoidance of exposure to cold and. (3) avoidance of tobacco.

Physical Medical Measures :—The application of local heat to the extremities deserves careful evaluation. Heat may be applied safely to a limb only by means of one of the accepted thermostat cradles. The temperature should never exceed 95° F. A helpful means of determining the safety of direct heat is the caudal or lumbar parasympathetic nerve block. If a rise in temperature of 4° F or more following the block is noted, controlled heat is probably safe and may be comforting. If there is no temperature elevations, the use of heat would undoubtedly be painful and frequently injurious. In contrast to direct heat, the application of reflex heat is a safe method and may be beneficial. This may be applied by means of the sitz bath or the use of a heating pad or cradle over the abdominal and lumbar regions. Short wave diathermy may be applied safely when used reflexly.

Some patients with severe arterial insufficiency are relieved of their pain by the application of cold. In these patients gangrene usually develops and they require surgical intervention regardless of treatment . Cold as a preoperative form of relief is beneficial but should not be used with the expectation of saving the limb.

Though vascular exercises as suggested by Buerger and Allen have been used as a routine by some, recent work seems to indicate that they may not only be valueless, but actually harmful.

The authors believe that the Sanders oscillating bed is one of the best mechanical devices for the treatment of occlusive arterial disease, especially for the treatment of edema and rest pain. The whirl-pool both is helpful in treating certain ulcerative lesions as crusts and necrotic tissue are gently removed.

Sympathetic Nerve Blocks and Sympathectomy :–Lumbar paravertebral procaine blocks have been used for a long time both as a diagnostic aid and therapeutic measure. It is of value in determining the degree of vasodilatation that may occur but should not be the sole criterion for sympathectomy.

The authors, as a general rule, have replaced the use of repeated blocks with sympathectomy when there is no contraindication to surgery. They, however, find a caudal block a more effective therapeutic measure. Nerve block by one or other measure is essentially helpful in temporarily relieving pain, in determining the value of sympathectomy and as a form of therapy when surgery is contraindicated. Sympathectomy is a surgical procedure of merit after conservative measures have been given an adequate trial and in certain instances where sympathetic nerve blocks have resulted in clinical improvement with a consequent rise in skin temperature. Patients with thromboangitis obliterans respond better than those with arteriosclerosis obliterans.

Medical Measures :—In discussing these, the importance of local foot hygiene should not be minimised. The use of vasodilator drugs has received attention for many years but, as yet, there is no drug that has proved consistently satisfactory. Adequate reports are not available regarding the use of ACTH and cortisone but Allen states that he noted no improvement in a limited number of cases. Recent reports about the new hydrogenated ergot alkaloids merit additional investigation. The routine use of the anticoagulants in cases of uncomplicated peripheral vascular disease is not recommended. The use of intra-arterial heparin, and more recently, intra-arterial heparin in conjunction with endarteriectomy, have opened up a new line of approach and the results to date appear encouraging. Work is also in progress concerning the use of low cholesterol, low fat diet, combined with lipotropic and endocrine agents.

EUSTACE J. DE SOUZA.

THE MANAGEMENT OF INTUSSUSCEPTION IN INFANTS AND CHILDREN, Moore, T. C. : Ann. Surg. **135** : 184-1952. 20 refs., 4 tables.

1. The literature concerning intussusception in infants and children is briefly reviewed.

2. Forty-three cases of intussusception are reported and divided into two age groups, infants and children, for the purpose of illustrating certain interesting clinical

and pathological features, wherein the two groups differ.

3. The experience with attempted non-operative reduction in 17 cases is discussed and the limitations of the method are cited.

4. Of the 37 patients under two years of age, the average duration of symptoms was 36 hours snd the mortality 18.9 per cent. None of the patients treated during the first 24 hours of symptoms died.

5. Two of the six patients over two years of age died post-operatively. One patient with lymphosarcoma of the terminal ileum is living without recurrence nine years after reduction of the intussusception and resection of the terminal ileum supplemented by post-operative radiation therapy.

6. Demonstrable precipitating pathology was encountered in eight of the 43 cases ; Meckel's diverticulum in four, polyps in two, lymphosarcoma of the terminal ileum in one, and duplication of the terminal ileum in one.

7. The speed with which the intussusception is recognised and effectively treated is unquestionably the most important factor influencing the outcome.

Author's Summary

EUSTACE J. DE SOUZA.

PEDIATRIC EMERGENCIES, Ellis, R. W. B. : Practitioner **168** : 338-346, 1952. 2 figures, 4 references.

The author deals mainly with those emergencies encountered during the first year of life with particular emphasis upon the new-born period.

Asphyxia and Apnea :—Failure to establish respiration satisfactorily at birth or to maintain it during the neonatal period is a symptom of a wide variety of conditions and carries grave risks to the infant. Recently emphasis has been placed not only on the infants colour but also on other evidence of shock. In the treatment it must be kept in mind that the infant's primary need is for oxygen. In clearing the air passages at least three sterile mucous extractors should be available and they should be fitted with rubber tips (a soft rubber catheter). In more severe cases direct laryngoscopy and the passage of a catheter into the larynx may be necessary. Immediately after birth a stream of oxygen may be played directly on the face which serves the double purpose of peripheral stimulation and ensures that with the first gasp the infant recieves a breath rich in oxygen. Another temporary measure is the use of a funnel or mask where oxygen may be administered at a pressure of not more than 15 mm. Hg. Oxygen through an intratracheal catheter requires the use of skilled hands. . Where oxygen is required for longer periods as in the case of small prematures a tent is necessary. The use of 5 per cent CO_2 in oxygen may be substituted for pue oxygen for short periods in the case of infants who have already breathed but in whom there is persistent atelectasis and recurrent apnea or irregular breathing. In the case of infants who have not breathed at all, good results have been claimed for the administration of oxygen by the gastro-intestinal route. Two No. 10 Nelation rubber catheters are passed into the stomach. One is connected to the oxygen cylinder and the second serves as an overflow to prevent overdistension of the gastro-intestinal tract. Artificial resuscitation must be used with care. Eve's rocking method may be safely used except when there is a possibility of intracranial hemorrhage. Mouth to mouth insufflation has long been used. Phrenic stimulation appears to offer a more physiological approach to the problem. General measures must not be forgotten and include warmth and respiratory stimulants.

Intestinal Obstruction :—Though the treatment is essentially a matter of skilled surgery the prognosis is largely determined by early recognition. In esophageal atresia the most common type is that where the esophagus ends as a blind pouch and the lower portion forms a fistula between the trachea and stomach. The first symptom will be vomiting or "bubbling" of air and mucus from the mouth. The gentle passage of a small esophageal catheter will usually demonstrate that the esophagus ends blindly and confirmation can be obtained from antero-posterior and lateral roentgenograms. Barium should never be given for diagnostic purposes as it will enter the lung and result in inhalation pneumonia. Duodenal atresia though less common than pyloric stenosis should always be borne in mind. Here the vomiting which may become projectile and be associated with visible peristalsis starts with the first feed. The vomitus contains bile if the obstruction is below the ampulla and the meconium will be colourless and will contain no vernix caseosa. Confirmation may be made by a straight film where it will be seen that the stomach contains air but the gut below is airless. Imperforate anus and rectal atresia should be sought for in every infant and failure to pass meconium within 24 hours should be thoroughly investigated since vomiting and distension may not occur till later.

Intussusception :—This rarely occurs in the neonatal period the peak incidence being between five and seven months of age. The first and most characteristic symptom is the sudden onset of attacks of severe coliky pain at intervals of about twenty minutes. Rectal examination within a few hours of onset may reveal blood on the examining finger. Absence of blood, however, should not contraindicate the diagnosis. The most important diagnostic sign is the presence of a palpable lump. Hemorrhagic Disease of the Newborn :—In this somewhat ill-defined condition, hypoprothrombinemia is an essential finding and treatment includes the correction of this by the administration of vitamin K. Although it has not been shown conclusively that the administration of vitamin K to the mother before delivery effectively prevents hemorrhagic disease in the infant, it appears rational to administer vitamin K immediately before delivery to women in whom a difficult or premature labour is expected. In treating the infant in whom hemorrhage has already occurred 5 mg. of vitamin K should be given immediately by injection and repeated again in four hours or again if necessary. Where hemorrhage has been enough to produce shock or where the hemoglobin has fallen below 60 per cent, immediate transfusion is imperative.

EUSTACE J. DE SOUZA

DERMATOLOGY

PERIARTERITIS NODOSA, Carric, L., and Heide, E. C. V. : Arch. of Derm. and Syph. 64 : 359-362, 1951. 2 photographs.

Periarteritis nodosa is a general disease with constitutional and cutaneous manifestations. The latter vary from simple erythema to erythema multiforme or erythema nodosum, urticaria, and even purpura. The lesions occur as nodules along the course of a superficial artery and manifest as subcutaneous nodules which are usually tender. These nodules may become vesicular, pustular or necrotic. Systemic manifestations pertain to the organ involved. Constitutional symptoms consist of irregular fever, tachycardia, weakness and acute pains in various regions. The course of the disease varies from mild to severe and recoveries have been recorded. On the basis that para-aminosalicylic acid was found useful in another collagen disease, *viz.*, lupus erythematosus disseminatus, the authors tried the same drug in their case with satisfactory results.

The author's patient was a 58 years old man, having painful, vesiculobullous, tender ulcerated lesions on both legs and feet. He complained of weakness and difficulty in walking upstairs. His blood pressure was 100/64. The following was the punch biopsy report : necrosis of the epidermis ; corium contained thick-walled blood vessels surrounded by infiltrate two-third of which consisted of eosinophils. The vascular walls often showed necrosis of "fibrinoid" degeneration. This was diagnostic of periarteritis nodosa. The blood smear differential count showed only 4 per cent of eosinophils. Treatment with pamisyl was started as follows : 1 tablet (0.5 Gm. each) four times on the first day, 2 tablets q.d.s. second day, till 6 tablets 4 times a day were reached. This was the maintenance dose and was continued for 12 months. Only 2 per cent diphen-hydramine cream was used locally to control the pruritus. Lesions healed completely at the end of 11 months and the patient regained his strength. Treatment was ambulatory throughout. There were no complications from pamisyl (P.D. & Co.) except an occasional loss of appetite.

T. K. MEHTA.

ANTIHISTAMINIC LOTION FOR MILIARIA, Schultheis, D., Flushing N. Y., and Traub, E. F. : Arch. of Derm. and Syph. **64** : 635-636, 1951. 4 references.

Miliaria was a difficult problem in members of the armed forces. The authors thought of the topical use of the antihistaminics. So far they were used by them in ointment form and as iontophoretic agents. Their effectiveness in ointment base is questioned by Perry. Therefore, the authors used benadryl (2%) in a standard lotion. The standard lotion consisted of 3 per cent salicylic acid, 4 per cent glycerine, 1 per cent phenol, 0.25 per cent menthol and alcohol 95 per cent. Two hundred subjects were used for the evaluation of results with the standard lotion, and the standard lotion with 2 per cent benadryl. The lotions were applied 3 times a day. The average duration of treatment was 5 days. From the study, the authors concluded that the basic alcoholic lotion which has been used in the treatment of miliaria can be much improved by the addition of 2 per cent diphenydramine.

T. K. MEHTA.

CORTISONE AND CORTICOTROPIN (ACTH) IN TREATMENT OF SCLERODERMA, Kierland, R. R., and Hines, E. A. : Arch. of Derm. and Syph. **64** : 549-554, 1951. 1 reference and 4 case reports.

Cortisone and ACTH have been employed in a variety of unrelated and intractable diseases, including the so-called collagen group of diseases. Scleroderma belongs to this latter group. The authors treated four cases, all females of the child bearing age (21 to 36 yrs.), with cortisone and two additional females with corticotropin (ACTH). The text includes detailed reports of all the four cases treated with cortisone and mentions two others treated with ACTH. The former was employed in the dosage of, on an average, 100 mg. daily, for 10 to 30 days, in a number of courses (4 in all in the present reports), at varying intervals depending upon how early the relapse occurs. It was administered parenterally.

The authors make the following observations from thier experience with their patients. It is a known fact that there is no specific treatment for scleroderma which is disabling, mutilating and painful and may produce death. Before the advent of cortisone, its treatment consisted of physical therapy, vasodilators, neostigmine, testosterone, *etc.* without tangible benefit. All the four patients who suffered from acrosclerosis (a type of scleroderma) with Raynaud's phenomenon, exhibited marked improvement on cortisone therapy. There was much more subjective improvement than objective. The authors ascribe this subjective improvement to euphoria consequent on cortisone therapy which was noted in all patients. Symptoms relapse on stoppage of therapy but remit on restarting the drug, in less time, and with a smaller total dosage. This suggests the necessity of finding a maintenance dose to achieve lasting benefit. But here the authors sound a note of warning that cortisone cannot be administered in moderate or high doses for long periods without the potentiality of development of toxic reactions. ACTH was not effective in the two patients for whom it was used. The authors ascribe this to improper dosage and administration. Finally they conclude that "cortisone provides the most pronounced clinical benefit of any agent yet used in the treatment of scleroderma, producing definite remission of symptoms of varying duration ; yet it does not cure the scleroderma" as evidenced by persistence of histopathological changes. They also point out the fact, observed by others as well, that cortisone should not be used during acute infections. There is no mention about the toxic effects of the drugs in the present series.

T. K. MEHTA.

PROGESTERONE THERAPY OF ACNE, Lewis, H. M., Frumess, G. M., and Henschel, E. J. : Arch. of Derm. and Syph. 64 : 562-564, 1951.

On the basis of results achieved by Way and Andrews, the authors instituted progesterone therapy for 12 patients with acne, resistant to the usual treatment for this disfiguring malady. Progesterone was administered substantially once a week for about 12 injections in the dosage of 6.6 mg. The encouraging results, to the tune of 75 per cent of cases, obtained by the aforementioned workers, were not duplicated. There was excellent improvement only in one, and a good response in another case. The rest failed to improve under this therapy. The authors conclude with a consoling note : "It is possible that our rigid selection of therapeutically nonresponsive patient accounts for the poor results obtained."

T. K. MEHTA.

PODOPHYLLOTOXIN, TREATMENT OF MICROSPORUM AUDOUINI SCALP INFECTIONS, Young, C. J. : Arch. of Derm. & Syph. 64 : 606-610, 1951. 13 references, 2 figures.

Tracing the history of podophyllin therapy, the author refers to the work of Kaplan who in 1942 reported the topical application of podophyllin the resin obtained from the root of *Podophyllum peltatum*, to be effective against condyloma acuminata. Besides, podophyllin has been found of value on local use, in the following skin conditions : granuloma inguinale, basal cell carcinoma, and scalp infections due to *Microsporum lanosum* and *M. audouini*. Podophyllin inhibits mitosis, and acts as a direct cellular toxin. Podophyllotoxin is the active principle of podophyllin and its content of commercial podophyllin resin varies from 28 to 52 per cent. Therefore for uniform results, it is necessary to use crystalline podophyllotoxin.

After testing successfully the *in vitro* effect of crystalline podophyllotoxin on hair infested by *M. audouini*, the author tried the drug in 14 patients suffering from tinea capitis due to *M. audouini*. The condition in nine of them was present for more than a year and had not responded to four months' treatment with 5 per cent calicylanilide ointment. The duration in the remaining five was not known and they received no other treatment previously. The therapy consisted of daily applications (excluding Saturday and Sundays) of 3.3 per cent podophyllotoxin massaged into the scalp avoiding entry of the drug into the eyes. Nine patients (64%) were clinically and mycologically cured in 30 days. Re-examination at one and two month intervals showed no fluorescence under Wood's Light, and skin cultures and hair cultures were negative for the fungus. Cures were observed in patients of all ages between 6 and 12 years. Folliculitis occurred in 9 patients and other cutaneous reactions occurred in five of the cured patients. Treatment was continued inspite of these reactions. The author points out that the percentage case with their method was higher than with other methods of treatment. The cures obtained were due to the direct fungicidal ability as well as through the follicular reaction produced by the agent. It is pointed out by the author that tinea capitis does clear up spontaneously at puberty, probably due to the production of monobasic normal aliphatic acids. In conclusion the author hopes that the investigation will be repeated on a large series with proper control studies.

T. K. MEHTA.

TREATMENT OF LUPUS VULGARIS BY INTRALESIONAL INJECTIONS OF CALCIFEROL, Russel, B. : Arch. Derm. and Syph. 64 : 676-683, 1951. 12 references, 3 figures.

On review of the systemic calciferol treatment of lupus vulgaris, the author observes that there is general agreement today regarding the efficacy of the former in the latter. However there may be refractory cases which respond to combined therapy with calciferol and streptomycin. This combined therapy is especially useful for severe and widespread resistant conditions, perhaps involving the nose and antrum and for those which are secondarily infected. But for patients with more localized resistant and recurrent conditions the author tried intralesional (local) injections of vitamin D2, in nine such cases which had resisted previous systemic calciferol therapy

The local intralesional treatment was given as follows :

Injections were given at intervals of one, two or three weeks. The volume of the injections depended on the size of the lesion, and on any one occasion, it never exceeded 600,000 I.U. vitamin D2. In small lesions it was given through an intradermal needle with a short bevel, in a volume sufficient to cause blanching and edematous hardening of the dermis. The local therapy was tried in nine cases. Clinical clearance resulted in six, two others were greatly improved and one proved resistant.

The advantages of this treatment are its consistent effectiveness and the smaller total dosage with freedom from side effects and less expense. Its chief disadvantage is the pain associated with injections. It is impracticable for extensive lesions or for those involving the mucous surfaces. Intralesional injections of vitamin D2 are indicated for (1) small localized lesions, particularly in children , (2) refractory lesions, (3) recurrent localized nodules, (4) patients intolerant to systemic calciferol, and (5) patients with concurrent pulmonary tuberculosis, cardiovascular disease, or renal diseases, or pregnancy, all of which are contraindications for systemic calciferol therapy.

As for the modus operandi of calciferol in lupus, little is definite. It is unlikely that it works only by producing a tissue reaction, otherwise it should prove useful in syphilis and leprosy. It probably has, directly or indirectly, an inhibitory, or even destructive, effect on the tubercle bacilli themselves *in vivo* and so enables fibrosis and repair to proceed. Exudative lesions usually respond best, especially if a brisk inflammatory reaction follows the injection. The method is usually effective in bringing about a clinical cure, but according to the author, further prolonged observation will be necessary in order to evaluate it by the more exacting standards of histologic and bacteriologic cure.

T. K. MEHTA.

CLINICAL EVALUATION OF "DIPHENYLPYRALINE" AS AN ANTIFUNGAL AGENT, Sokoloff O. : Arch. Derm. and Syph; 64 : 754-756, 1951. 2 references, 1 table.

It was known that "diphenylpyraline," an antihistaminic, possessed an *in vitro* antifungal action against a variety of fungal organisms. In order to provide the clinical confirmation, the author tried the drug in various fungus affections of skin. The drug was used in two forms as 2 per cent solution in tap water and as 2 per cent ointment in standard ointment base. The former was used in wet, oozing, inflammatory eruptions and the latter for dry ones. The drug was applied twice a day. The results can be best appreciated from the appended original table.

Results of Use of Diphenylpyraline in Treatment of Fungal Infections.

Diagnosis.	Organism.	Case Nos.	Response.
Tinea pedis	*T. gypseum* *T. purpureum* *E. inguinale*	25 9 3	Excellent clinical response with no untoward reaction in all 37.
Tinea cruris	*E. inguinale*	26	Excellent in 24 ; No response in one ; local irritation in one.
Tinea corporis ..	*M. lanosum* *T. gypseum*	9 4	Excellent in all 13, No reaction.
Tinea axillaris ..	*T. purpureum*	2	Excellent ; no reaction.
Tinea capitis ..	*M. audouini* *M. lanosum*	10 4	No benefit. Excellent response.
Tinea versicolor ..	*M. furfur*	2	Excellent.
Oxnchomycosis ..	*T. Purpureum* (*rubrum*)	6	No response.
Monilia intertrigo ..	*M. albicans*	2	Excellent.
Tinea sycosis & barbe	*T. gypseum*	1	Excellent.

Of all the cases, those of tinea pedis responded most dramatically. Some of them were of very long duration and resisted usual antifungal treatment. The author gives no idea as to what was the average duration of cure and whether there were relapses. Besides the antifungal action of diphenylpyraline, its local anesthetic action also helps a great deal in bringing about clearance of tinea. Inspite of the encouraging results obtained, the author feels that further corroboration is required for fully establishing the antifungal utility of the drug.

T. K. MEHTA.

TREATMENT OF URTICARIA AND DERMATITIS VENENATA WITH CORTICOTROPIN (ACTH) AND CORTISONE, Captain Ekblad, G. H.: Arch. Derm. and Syph. **64** : 628-634, 1951. 4 references 3 tables.

After reviewing the literature, the author details the results of treatment with corticotropin (ACTH) and cortisone tried in (*i*) acute urticaria, (*ii*) chronic urticaria and (*iii*) allergic dermatoses. There were 15 cases in the first group, 11 of which were due to allergy to penicillin. In the remaining four acute urticaria was due to a sulfonamide drug, a food allergy, paint fumes, and an undetermined cause, respectively, In 12 of these cases of acute urticaria ACTH was administered, 10 mg. every 3 hours. for four doses only. Except for 2 cases (where dosage was smaller) all patients were uniformly benefited. There was a good response to cortisone also but it appeared to be less effective than corticotropin. It was given in the dosage of 25 mg. 4 times.

Anti-histaminics (benadryl) used in conjunction with intravenous calcium gluconate were of definite but transient benefit to some patients of acute urticaria. Corticotropin and cortisone are definitely superior to the latter combination.

There were five cases of chronic urticaria in three of which no cause could be found out. Of the remaining two, one was due to tetanus toxoid and the other was due to amebiasis and hepatitis. In the above dosage schedule ACTH (10 to 20 mg. 4 times) and cortisone were disappointng in chronic urticaria. As regards allergic dermatoses, both corticotropin and cortisone were useful to the extent of relieving symptoms in severe acute dermatitis but they did not shorten the healing period. Thus their use is recommended in very severe cases.

T. K. MEHTA.

RESULTS OF TREATMENT OF ACNE VULGARIS BY INTRAMUSCULAR INJECTIONS OF VITAMIN A, Mitchell, G. H., and Butterworth, T. : Arch. Derm. and Syph. **64** : 428-430, 1951. 9 references.

In this article the authors report their own results after reviewing the available literature on the subject. The previous specialists like Sulzberger, Obermayer and others gave vitamin A by mouth in daily dose of 100,000 units. They emphasized the point that acne which is characterized by prominent follicular plugging in addition to the formation of comedos, responds most readily to this form of therapy. Besides, they point out the necessity of continuing the treatment at least for 3 to 6 months before it is given up as ineffective. Most of the workers noted marked improvement in from 50 to 90 per cent. of cases. All of them used oily solution of vitamin A.

In contrast to this the results obtained by the authors in their series were unfavourable. The series comprised of 30 patients divided into 3 groups of 10 each, and consisting of equal number of boys and girls of adolescent age. 100,000 units of water soluble vitamin A was injected intragluteally, thrice a week, to the first group, for a total of 20 injections. The second group of 10 received similar treatment with vitamin A in oil. The third group of 10 served as a control with no vitamin A given to them. The authors noted that at the completion of treatment only 2 of 30 showed any marked improvement and concluded that it was useless. Besides, aqueous preparations were more painful locally and gave rise to hot, swollen, tender buttocks. It was interesting to note that those receiving only vitamin A fared worse than the control series. It may be noted that treatment period lasted only little more than 6 weeks.

Results of Treatment of Acne by I. M. Inj. of Vit. A.

Type of Treatment.	No. who were better.	No. who were worse.	No. who were the same.
Vitamin A in oil	2	4	3
Vitamin A in water	1	1	8
Control (No. Vitamin A)..	2	2	7

T. K. MEHTA.

VENEREOLOGY

GRANULOMA INGUINALE : FURTHER OBSERVATIONS ON RESULTS OF TREATMENT WITH AUREOMYCIN AND CHLORAMPHENICOL, Robinson, H. C. V., and Cronk, B. : Am. J. of Syph. Gon. and Ven. Diseases **35** : 378-382, 1951. 8 references, 2 tables.

After reviewing the available literature on the subject, the authors narrate their own experiences with the two new antibiotics and report the results in a tabulated form. 42 Negro patients were treated with aureomycin in four different dosage schedules.

Results of the treatment can be better appreciated from the appended tables.

Results with Aureomycin

	No. Cases.	Total Dose.	No. Healed.	Average Period of Healing in days.	No. Relapsed
Group I	7	1.0 Gm. I.M.	4	491	3
Group II..	12	4 to 9 Gm. Oral	2	493	9
Group III	8	20 Gm. Oral	3	308	4
Group IV	15	40 ,, ,,	8	338	6

Results with Chloramphenicol.

	No. Cases.	Total Dose.	No. Healed.	Average Period of Healing in days.	No. Relapsed
Group I	4	20 Gm. Oral	2	33	2
Group II..	12	40 ,, ,,	10	118	2

Group I treated with less than 1 Gm. aureomycin by intramuscular route shows significant results and these are in contast to findings of Greenblat's group. However, the authors are silent on its routine use. From the above 2 tables the authors have arrived at the following conclusions : (*i*) Very high relapse rate, probably due to more prolonged observations ; (*ii*) No "cure rate" estimation can be formed from the small series ; (*iii*) A year should elapse from the time of treatment with these drugs before permanent healing can be expected ; (*iv*) no concrete opinion can be formed regarding utility for these drugs till more study is forthcoming ; (*v*) chloramphenicol brings about more rapid healing and may eventually yield a higher cure rate than aureomycin.

T. K. MEHTA.

The Phoenix Cancer

"Cancer research has reached a stage at which the following affirmations can be safely made.

"The exciting causes of cancer are multiple and complex. In fact cancers may now be induced experimentally at will by (a) genetic manipulations *i.e.* inbreeding, selecting and cross-breeding, (b) injection or feeding of any of several hundred chemicals, some of which are organ specific, (c) hormonal imbalances and disturbances, (d) many of the energy agents (roentgen, gamma, radium and ultraviolet rays) especially in animals that are subjected to interval exposure, and (e) a combination of two or more of the aforementioned factors. It seems unmistakably clear that no single specific agent or condition or any combination of agents or conditions is responsible for the initiation of all types of cancer." My view might be put in the form of a three-act play.

Act 1. Frontier town. Oppression by foreign thugs called carcinogens. Communist rising which is quelled by regular troops. (Interval of twenty years).

Act 2. Capital city. Decline and fall of the reigning house—the gonads.

Act 3. Frontier town again. The old grievance resurrected. Communist rising again. Successful spread throughout kingdom. Dissolution, Curtain. Medical World. 75: Jan. 4, 1952.

EDITOR RETIRES

The issue of the Journal marks a change of editorship with the resignation of Dr. George Coelho. The Indian Journal of Medical Sciences has grown out of the former Medical Bulletin of which Dr. George Coelho was the editor since its commencement. The Editorial Board was reorganised with the foundation of the Indian Journal of Medical Sciences in 1947, and Dr. Coelho was unanimously elected as its editor. The Editorial Board accepts with great regret Dr. Coelho's resignation which has been necessitated due to other important preoccupations. Dr. Coelho is still, however, a member of the Editorial Board.

The Editorial Board would however like to record the memorable services of Dr. Coelho to this Journal as he was mainly responsible for its growth into its present status.

The Editorial Board looks forward to the continued success of the Journal under the leadership of its new editor Dr. J. C. Patel who has been an active member of the Board since its re-organisation.

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NATURAL HISTORY OF TYPHUS FEVERS IN INDIA *

S. L. Kalra †

The natural history of typhus fevers in broad outlines will be the same anywhere, but geographical differences can introduce local departures. It is the purpose of this paper to review the work carried out in India, with particular reference to any such departures.

EPIDEMIC TYPHUS

In 1808, according to Eyre,[4] fifteen cases of typhus were admitted in His Majesty's hospital at Ghooty. This was the earliest record that could be traced in Indian literature. From 1852 to 1915, at least 22 papers were published describing typhus cases from different parts of the country like Mianwali, Ajmer, Lucknow, Agra, Bombay, Madras, *etc.* In those days every case of typhus was regarded as louse-borne, but from the epidemiological accounts it was clear that more types than one were mixed up.

The outbreak at Saugor, in 1859, and at Jubbulpore, in 1865, described by Wright,[20] and based on the reports of Major W. R. Rice, were definitely of epidemic typhus. Rice states that "during this fever, hospitals were established in the city of Saugor, and in the cantonment bazar, because whole families were stricken at once and none were left to nurse the sick". It started in the European community and spread to the locals. Possibly the infection was imported from England. Zinsser[21] mentions an outbreak in London in 1862. Importation of infection from one distant country to another had occurred even in the days of slow moving ships, for rickettsia can survive in louse fecal dust or a case of Brill's disease may start an epidemic in a louse infested community.

Hendley[6] has stated that he saw 9 epidemics in 15 years in the Peshawar valley, and that it was endemic in trans-Indus districts from Ysufzai,

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* Paper read at the Annual Conference of the Association of Pathologists of India, at Hyderabad, in November 1951.

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Hazara to the Himalayan foot hill tracts in Kulu. The starter case in the 1991-92 outbreak at Peshawar was traced by him to Kabul. In the same year at upper Kulu there were 626 deaths from typhus from January to March. Husbands and Macwaters[7] have described an outbreak in the 1st. Mule Corp at Peshwar which had just returned from a mission in Tibet. According to Kalra and Rao[9], there was an epidemic in Kashmir in the winter of 1943-44 started by the entry of Kazaks from Russian territory ; and another in the winter of 1947-48. In the last one there was no evidence of importation from outside but circumstances had provided suitable conditions for its spread. This time *R. prowazeki* were isolated from patients and lice.

From the accounts of the last century, it appears that scattered outbreaks of epidemic typhus were not infrequent in the plains of India; and the endemc belt started from Baluchistan and ran in a geographical continuity through the northern hills and Kashmir to the Kulu valley. In the beginning of this century it disappeared from the plains but remained in this northern belt. For in the plains the unsuitable climate, aided by improvement in personal hygiene, due to the cheap availability of soap, have reduced the vector to below dangerous numbers : but conditions in Kashmir, *etc.*, have remained unchanged.

MURINE TYPHUS

The cases described by Quill[13] at Deolali and Bradley and Smith[1] at Jaffurpur were isolated ones. There was no evidence of contagion in the cases at the residency during the siege of Lucknow, described by Greenhow[5]. Chakarbutty[2] at Calcutta came across cases in Europeans and Indians residing in different parts of the city, and failed to find any evidence of contact. Rice has mentioned that in the Jubbulpore district single cases occurred in families. In the last 25 years, cases have been described by other authors, and recently, rickettsia have been isolated from patients in many places. Savoor, Soman and Vahia[14] isolated strains from patients in Bombay. Kalra and Rao[9] recovered strains from patients at Jubbulpore, Bangalore, and Kashmir, and Kalra from patients at Lucknow and Poona. The incidence in the army from 1943 to date shows that it is present in all parts of the country.

Vector and Reservoir :—In India, infection is harboured not only by rats but also by bandicoots. Savoor, Soman and Vahia,[14] and later Soman[16] isolated rickettsia from rats in Bombay. Stoker[17] found infection in rats in Poona. Earlier, Covell[3] and Webster[19] recovered *R. mooseri* from rats in the Simla hills. Kalra and Rao[9] recovered *R. mooseri* from rats at Jubbulpore, Bangalore, Mysore, Srinagar; and from bandicoots at Bangalore.

The insects found infected in nature in India are more than one. Strains from mixed pools of more than one species of rat-fleas were recovered by Kalra and Rao[9] at Jubbulpore, Bangalore, Nanjangud, Kashmir ; and from a pool of *X. brazilliensis* only, at Mysore.

Ticks, *Boophylus australis*, collected from bushes at Khamaria, a suburb of Jubbulpore, were found infected with *R. mooseri* by Kalra and Rao[9]. In Kashmir, two strains of *R. mooseri* were recovered from lice collected from patients who were suffering from urine typhus. The lice, after collection from the patient, were stored in the laboratory and were examined when the blood in their body was digested.

Seasonal Incidence :—The incidence throughout the country was not high during the same months, but in corresponding periods of more or less identical weather. The correlation was more with the mean monthly minimum temperature than any other climatic factor. Taking three places, like the Kashmir valley, Jubbulpore and Bangalore, the highest incidence, respectively, was in the months of May, November and January, when the respective mean minimum temperature was 50.5° F, 52.0° F and 57.0° F.

TICK TYPHUS

Megaw[10] first suspected ixodidae ticks as one of the vectors in India, when he himself got typhus 20 days after he was bitten by a tick near Bhimtal. Later in the next 7 years, along with other authors, he described 50 cases out of which 12 had a history of tick bite. Then three other authors, in 1932-33, described 17 cases with evidence of tick bite in 3 patients.

The case against the tick was, so far, circumstantial, which may not be always true. Kalra and Rao[9] have cited the case of Lt. Col. Indersby at Jubbulpore who was bitten by a tick 8 days before he developed typhus, but his blood gave a positive complement fixation test with murine antigen, and was negative with rocky mountain spotted fever antigen. Also, the ticks collected from near his house were infected with *R. mooseri.*

However, by now, ticks have been found infected in nature. Kalra[8] isolated a strain from *Hemophysalis leechi var indica* at Imphal and from *Ixodies ricinus* at Almora; Kalra and Rao recovered a strain from *Rhipecephalus sanguineus* at Srinagar. The last strain was studied along with workers at the Rocky mountain laboratory in the U.S.A., (Philip *et al.*[12]) and was found to be more close to boutonneuse fever rather than rocky mountain spotted fever but not exactly identical with any one of them.

Strains of tick typhus have also been isolated from patients by Kalra and Rao at Jubbulpore, by Rao at Srinagar, and Kalra at Poona. Topping, Heilig, and Naidu produced serological evidence of tick typhus at Mysore. If cognizance is taken only of those cases where the diagnosis was established by the complement fixation test or by the isolation of rickettsia, then one can say that it is present in many parts of India, but the incidence is the lowest of all other typhus fevers.

The recorded incidence in literature is so little, that no statement can be made about its seasonal prevalence. Surveys of the Seoni and Chindwara forests in the Central Province showed that tick density increased during the rains, remained high during the mild winter, but was rapidly lowered with the approach of the hot and dry summer. It is probable that, at least in these parts, the seasonal incidence of tick-typhus follows the same course.

The name Indian tick-typhus or just tick-typhus is justified, for the only strain properly studied was near boutonneuse but distinct from it. Moreover, the vector of boutonneuse fever is *R. sanguineus* only, but in India two other species besides this have been found infected in nature.

SCRUB TYPHUS

In 1933, A. H. Q. (India) directed all army laboratories to carry out the Weil Felix test as a routine in all fevers. From the data collected in one year, it was summarised in the Annual Report of 1934 that scrub typhus is scattered throughout India, with a seasonal incidence in the late monsoons, from mid-August to the beginning of October. Further knowledge was added by Mehta[11] who found *T. delicnsis* larva on rats in the Simla hills. Webster[19] definitely established its existence by isolating rickettsia from a patient. Our knowledge was limited to these facts when the last war started.

From 1942 onwards, the incidence in the troops under SEAC began to increase rapidly. According to Sayers[15], there were 51 cases in 1942, the next year, 279, and in 1943 there were 3790 cases in Manipur state on roads radiating from Imphal. The urgent necessity of further investigation was felt, and research teams were raised. The information given below is abstracted from the reports of AHQ Field Typhus Research Team.

The Vector (*T. deliensis*) :—The larvae attach themselves on the inside of the ear of rodents and on the hind legs of shrews, but sometimes they may be found on any part of the body, particularly on the margin of the ear or the genitals. So far, they have been found in the Kumaon hills at Nainital, the Bhimtal lake area, Almora, Mukteswar, and Kausani ; in Kashmir state only, at Uri, Chaukibal, Teethwal, Gorez, and Kanzalwan ; in Central India at the Seoni and Chindwara forests ; in the south, at Poona, Kamreddy, Bangalore, Mysore, Nanjangud, Gudalur, Sultanpet, and the Chedleth forest.

If one presumes that *T. deliensis* is the only vector, then from the combined reports about the vector and cases, one can outline the distribution of the vector of scrub typhus in India as under. In the north it is present in the whole of the Suwalik range which extends from

Jammu to Assam; from there it has penetrated into the central Himalayas in which Gorez and Teethwal are situated, but has failed to reach or establish itself in the inner Himalayas which form Ladakh and Tibet. Zoogeographically, the Siwalik range is a part of the Indo-Chinese subregion, and this mite is present over the whole of this area. Towards the plains it extends to varying depths depending on the monsoons. In Bengal and Assam the typhus belt extends right up to the coast, from there as one proceeds westwards, it gradually narrows receding towards the hills. In Central India it is mainly confined to the Vindhya and Satpura ranges. In the Deccan it is thinly scattered all over with a high density in the forests of the Western Ghats.

It flourishes in vastly different climates, *e.g.*, coral islands at sea level near the equator, with uniform weather throughout the year; monsoon forests of the tropics with long dry spells ; at altitude of 9,100 ft. (Kanzalwan, Kashmir) in hills of the temperate zone, where winter temperatures are below freezing point and the ground gets covered with snow. The study of microclimate in the top soils may perhaps smoothen out the obvious differences.

The breeding of the mites suddenly increased when the monsoons began, therefore the disease was seasonal. A few cases occurred with the first rains, the largest numbers were in the late monsoons, and only stray cases when it came to less than 4 rainy days or less than 3 inches of rainfall in the month.

The natural mite colonies were in grass, scrub-land and hill-sides covered with scattered trees and thick under-growth. From there the irrigation channels and their networks have provided it with new routes of travel and spread, and suitable habitats. By now new colonies are established on many agricultural lands and fruit gardens.

Study of a typhus island of a small restricted area showed that the largest numbers of mites were on damp ground in scrub and on pond edges ; less under a tree base and the least in dry scrub. Their movements on the ground must be very restricted, for none of these spots were more than 9 feet distant from the other, but the catches were repeatedly in the same order.

Krishnan (personal communication) has shown that the infection is hereditary and he has traced it up to 5 generations so far. The mite, therefore, is not only a vector but an important reservoir. There was also some evidence that fresh lines of infection could be added by feeding clean mites on infected rats. In one experiment 5 batches of clean mites were attached to infected *Rattus rattus* with rickettsemia. Of these, two batches became infected. It showed that larvae could acquire infection from rats, though irregularly.

Animal Hosts of the Vector :—Different small mammals commonly infested in nature were various species of *Rattus rattus*, shrews ; bandicoots, tree shrews, field mice, *Tatera indica*, monkeys and a barking deer. Those that were infected in nature were *R. r. bullocki*, few other species of *R. rattus, Hadromys humei thomas, Tupaia belangari belangari, Bandicoota bengalensis, R. rattoides hodgson and Mus platythrix bennet.*

In laboratory experiments on *R. rattvs*, after a subcutaneous or intradermal injection, rickettsemia occurred after 3 days and persisted for a maximum of 74 days. From the brain, rickettsia were isolated up to 99 days, but isolations after 75 days were irregular. Three rats were re-inoculated 6 to 7 months later, when the blood had become negative. Rickettsemia occured again and persisted for 4 weeks or more. It showed that rats acted as temporary seasonal reservoirs and that infection in one season did not exclude them from this role next year. As rickettsemia in rats implied fresh infection, it was taken as a sign of active transmission in nature. This was repeatedly confirmed by field observations. In endemic areas during the typhus season, rickettsia were easily isolated from the blood of rats but not during the off season, when they were sometimes recovered from the brain only.

SUMMARY

Epidemic typhus used to occur in the plains of India, but has now disappeared. Rat fleas, ticks and lice have been infected in nature with *R. mooseri.* Tick-typhus of India though very near boutonneuse fever is slightly distinct from it, and 3 different species of ticks have been found infected in nature. The distribution of scrub typhus in India is outlined, and a study of infection in rats is summarised.

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"..........The medical profession has decided on the whole that its public shall not be informed. Its laity is, of course, encouraged to understand the elements of hygiene. It is not encouraged to occupy itself with medical science proper, or to indulge in anatomical introspection. In its impenetrable wisdom, the medical profession has decided that it is best if the patient cannot read its prescriptions. The patient can exercise his patience in the confident assurance that his doctor knows, and is doing, what is best. Far be it from me to question these decisions."—Prof. C. A. Mace, D. Lit., in his presidential address to the psychology section of the British Association, at Edinburgh on Aug. 9. Quoted from Lancet, 2: 288, 1951.

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"........When a patient cannot afford a complete medical service he is going to buy only that part of which he is in most urgent need......If we are to believe that there is a law of supply and demand as the economists tell us, the doctor is only going to stock those articles for which he has ready sale. Therefore, he is going to stock all the necessary knowledge and gadgets for giving appendix attention, or broken leg-attention, but he is not going to trouble very much about housing attention, nutrition attention, industrial work attention, and so forth. As a corollary to this, it is not surprising to find that, speaking broadly, the medical students are trained to give appendix attention but not housing attention. In other words, the Universities all over the English-speaking world train their medical students to be hospital house surgeons but not health officers, in obedience to the law of supply and demand based in a fee-linked service."—Dr. Albert Blanc, Money, Medicine, and Masses, Wellington, New Zealand, 1949, p. 130. (Quoted from Lancet, 2: 294, 1951).

UNUSUAL MANIFESTATIONS IN HUMAN POLIO *

P. V. Gharpure † and P. R. Bhatt †

I. INJECTION AND PARALYTIC POLIO—CASE REPORT

An account of a case of poliomyelitis with the development of paralysis in the limb last injected with quinine hydrochloride (intramuscular) in the right thigh is given below.

It has been reported that the injection of diphtheria[3] and pertussis and other vaccines in the arm in polio-epidemic induces paralysis first of the injected arm.

In the case now being reported cholera vaccine was injected in the arm but there was no paralysis of that arm. Paralysis precipitated in the lower limb in which was injected last (quinine hydrochloride).

CASE REPORT

A patient 2499/S.R.—Age 2 years and 8 months with paralysis of both lower limbs during the polio-epidemic of Bombay in August 1950 was noted with the following injection history :—

Date.	Injection.	Part injected.	Symptoms.
9-7-1950 ..	Cholera vaccine.	Was injected in the left arm (deltoid muscle)	For 3 days—pain in the left shoulder with fever and headache (9th, 10th & 11th July, 1950).
12-7-1950 to 16-7-1950	....	....	No Complaints.
17-7-1950 ..	....	....	Fever with rigors on alternate days (diagnosed as malaria, treated with quinine mixture. No change till 2-8-1950).
2-8-1950 ..	....	....	High fever, sore throat, headache and vomiting (no rigors and no pain in limbs).
3-8-1950 ..	Intramuscular quinine hydrochloride.	Right lower limb gluteal region.	Injection was given in the morning. Symptoms persisting.
4-8-1950 ..	....	....	Fever was low but continuous. No headache. Sore throat and vomiting present.

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* Paper read at the Annual Conference of the Association of Pathologists of India, held at Hyderabad, in November, 1951.

† From the Polio Research Unit of the Indian Council of Medical Research, Pathology School, Grant Medical College, Bombay 8.

Date.	Injection.	Part injected.	Symptoms.
5-8-1950 ..	Intra-muscular quinine hydrochloride.	Right lower limb lateral vastus muscle.	Injection was given in the morning. Fever was slight, no vomiting, and sore throat was only mild. The child was able to walk after the injection. On the same day, in the afternoon, the child suddenly developed flaccidity of the right lower limb (injected limb) and weakness of the left lower limb. The flaccidity in the right lower limb slowly increased thereafter.
10-8-1950 ..	....	....	Admitted to the B. J. Children Hospital, with flaccidity in right lower limb with weakness of the left lower limb and pain in the neck and back region.
14-8-1950 ..	....	....	Cerebrospinal fluid removed by lumbar puncture showed increased proteins, 45 lymphocytes per c.mm. Chlorides 740 mg. per cent and sugar normal.

II. A CASE REPORT OF TWO SUCCESSIVE ATTACKS SUGGESTIVE OF POLIOMYELITIS IN A HUMAN BEING IN THE SAME EPIDEMIC

A second attack of poliomyelitis is not common though it has been reported as a possibility. Such cases have been reported in the literature (Quigley[4], Bridge *et al.*[2] and Alves *et al.*[1]). The following case will therefore be of interest.

The appearance of a second attack raises the suspicion that immunity acquired after an attack of poliomyelitis may not be complete and lasting.

Mild atypical cases are unfortunately often missed ; in such circumstances it is very likely that atypical second attacks frequently go undetected. In the same way mild attacks preceding a recognised clinical attack may not be detected.

CASE REPORT

First Attack.

Clinical Features :—A male child, M. M., 18 months of age, was admitted to the Byramjee Jeejeebhoy Children Hospital, Bombay on 30-5-1950, during the earlier period of a mild poliomyelitis epidemic in Bombay. The child had running of the nose and cough for three days, followed by fever and convulsions on the 4th day. There was no history of any contact with a poliomyelitis case. On admission the child was unconscious and had flaccid weakness of the left arm, left leg, and the left side of the face. Twitching of the face was present for a day. The child regained consciousness after 5 days. The weakness of the face, the left arm, and the left leg lasted for about a month. The patient was discharged from the hospital on 9-7-1950.

Laboratory Findings :—The cerebrospinal fluid was under tension, in appearance it was clear, proteins were normal, sugar was normal, chlorides was 735 mg. per cent, cells were 15 per c.mm. (lymphocytes).

Animal inoculation.—The stool of the patient inoculated into the rhesus monkey intra-nasally had produced poliomyelitis which was further confirmed histologically.

Second Attack.

Clinical Features :—Towards the end of the same epidemic on 4-9-1950 (57 days after discharge from the hospital) the child was re-admitted to the hospital for cough and cold of 4 days duration. On 3-9-1950 the patient had high fever, unconsciousness, concussion and weakness of the right arm and the right leg, of sudden onset. There was also weakness of the neck and the muscle of the back with a bilateral ptosis. The child recovered completely from the flaccid weakness of the right upper and lower limbs after about two months. There, however, was mental deficiency and diminished vision with palor of discs of both fundii.

Laboratory Findings : The cerebrospinal fluid was under tension. The appearance was clear, sugar was normal, cells (lymphocytes) 15 per c.mm., chlorides were normal.

This time the stool was not collected for animal inoculation.

The question arises as to whether (i) the second attack was a result of re-infection from a new source or (ii) it was an auto-infection from the virus persisting in the bowel.

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If one is dead and wants to be cremated one must get a special certificate signed by one's own doctor and another signed by an independent practitioner of at least 5 years' standing. That is the law. A friend of mine was called in by a local colleague not long ago to act as certifier No. 2. The facts were straightforward. The deceased was elderly, had been known to the doctor for many years, and had been expected to die at any time. The two doctors walked into the house by the back door, entered the sickroom, glanced at the body after a peremptory lifting of the covering sheet, and duly affixed their signatures to the forms. The way to the front door was through a sitting-room, and there they found the whole family assembled. The son, who was the chief mourner, stood up, my friend was introduced, and in the embarrassed and subdued voice usual on such occasions he muttered tactfully : "How peaceful your mother looked!" The chief mourner's face dropped and a frown appeared on his forehead. The family doctor was seen to be signalling desperately; but it was too late. The deceased was—the father!

The story is true; that I know. I also know that my friend literally fled from the house, and he has since been absurdly finnicky about signing any slip of paper.

—In England Now, Lancet, **2**: 312, 1951.

CEREBROSPINAL FLUID FINDINGS IN MONKEYS INFECTED WITH KNOWN INFECTIVE POLIO MATERIAL*

P. V. Gharpure† and C. S. Swaminathan†

In experimental poliomyelitis, Flexner[1] has reported the findings in the cerebrospinal fluid in monkeys inoculated intranasally with the virus of poliomyelitis. A perusal of the available literature not having revealed any other published account dealing with this subject, we are presenting below our findings. An attempt is made to determine whether these findings are helpful in predicting, confirming or excluding a positive take in the inoculated animal.

The data presented below are of animals used in this laboratory for isolation and passage of the virus. A treated suspension of stools was used for the intranasal inoculation and an emulsion of the spinal cord for the intrathalamic inoculation. Following the inoculation, daily clinical examinations of the animals were performed to detect symptoms of the disease. The cerebrospinal fluid was obtained by a lumbar puncture in most cases. It was only in occasional instances that a cistern puncture had to be undertaken.

The cerebrospinal fluid was examined for cells and proteins soon after withdrawal. The interval between the collection and the examination had not exceeded 30 minutes. The cell count was made with the improved Neubauer counting chamber. The proteins were estimated by using a proteinometer. 0.5 cc. of the cerebrospinal fluid was added to 1.5 cc. of a 3 per cent sulpho-salicylic acid and the fluids mixed by inverting 6 or 7 times, and the opacity compared with the standard tubes. The predominant cell in the cerebrospinal fluid was not determined. Only the total cell count was done.

For convenience the animals were divided into the following groups, *viz.*,

Group I	Intranasal positives,
Group II	Intranasal negatives,
Group III	Intrathalamic positives, and
Group IV	Intrathalamic negatives.

Group I (*Intranasal positives*) :—The animals were inoculated by the intranasal route according to the technique advocated by Howe and Bodian[2]. Cerebrospinal fluid examinations were performed from the third day following the first inoculation in most animals. Six of the seven animals in this group have been finally confirmed as positive takes, clinically and histologically. Of the seven animals in this series, an increase in the cell count in the cerebrospinal fluid was as follows—(i) from 42 cells to 193 cells in two animals of the three examined on the third day ; (ii) from 85 cells to 88 cells in four animals of the five examined on the fifth day : (iii) from 90 to 147 cells in four animals of the five examined on the seventh day ; and (iv) from 50 to 620 cells in six animals of the seven examined on the ninth day.

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* Paper read at the Annual Conference of the Association of Pathologists of India, held at Hyderabad, in November, 1951.

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Protein estimations revealed an increase of total proteins ranging from 20 milligrams to 100 milligrams per cent whenever there was increase of cells.

Of the seven animals, six showed a definite increase in the cells and the protein content of the cerebrospinal fluid at a period when there was no obvious clinical symptoms—the only indication of infection being a rise of the temperature. In one animal, the increase of the cell count was noted simultaneously with tremors followed by a rise of the temperature. A cell count of 20 and over at any time after the last inoculation has been considered by us as suggestive of a take.

Group II (*Intranasal negatives*) :—As a contrast to the above findings there are thirty-six animals inoculated intranasally with the same type of inoculum and observed on the same plan as the animals of the first group.

Complete histological studies have been performed in five of these animals. These five animals were sacrificed at periods ranging from 6 days to 22 days from the last inoculation. These animals were histologically negative.

The remaining animals of this group were observed for periods ranging from sixty days and over after the last inoculation and were then utilised for other purposes.

In the animals of this group the cerebrospinal fluid findings were as follows—(i) of the nine examinations done on the third day after the last inoculation, the cell counts ranged between 1 and 4 cells. (ii) eleven examinations done on the fifth day revealed counts between 1 and 8 cells ; (iii) nine examinations done on the seventh day gave cell counts ranging between 1 and 8 cells ; (iv) twenty-three examinations done on the ninth day revealed cell counts ranging between 2 and 8 cells : and (v) one animal showed a cell count of 12 which was due to contamination with blood.

Protein values in the majority of the cerebrospinal fluids removed from animals of this group have remained at the level of 15 milligrams per cent and below.

Group III (*Intrathalamic positives*) :—In this group there were fifty-seven animals. These were inoculated by the intrathalamic route with 0.25 cc. of a 10 per cent emulsion of the cord. Among these animals cerebrospinal fluid examinations were done on the third, fifth, seventh and ninth days after the inoculation. (i) Cell counts in twenty-five animals recorded on the third day after inoculation gave values ranging between 3 cells and 2,560 cells with protein values ranging between 15 milligrams to 100 milligrams per cent. Five of these had cell counts below 20 and eight had protein values below 20 milligrams per cent. (ii) Five days after inoculation, cerebrospinal fluid examinations were done in thirty-one animals which showed cell counts ranging between 8 cells and 1,000 cells with protein values ranging between 10 milligrams to 100 milligrams per cent. Five of these had cell counts below 20 and five had protein values below 20 milligrams per cent. (iii) Seven days after inoculation, cerebrospinal fluid examinations done in twenty-four animals gave cell counts ranging between 20 to 910 with protein values ranging between 20 milligrams to 100 milligrams per cent. In two of these animals the cerebrospinal fluid clotted spontaneously, so that a correct cell count could not be obtained. (iv) Cell counts on the nineteen animals that were allowed to survive till the ninth day after the inoculation, ranged between 53 cells to 167 cells with protein values ranging between 30 milligrams to 100 milligrams per cent. The cerebrospinal fluid from one of these nineteen animals clotted spontaneously.

In the animals which were inoculated by the intrathalamic route a sustained increase of cells and proteins after the fifth day of the inoculation was concurrent with a positive take.

Group IV (*Intrathalamic negatives*) :—The number of animals studied under this group is twenty-four. In these animals inoculated intrathalamically, and which were negative, either histologically or clinically for a period of one month and over, marked pleocytosis was not noticeable, as a rule, after the fifth day of the inoculation. Cerebrospinal fluid examinations on the fifth, seventh and ninth day revealed in most of the animals cell counts not exceeding 20 cells and protein values of 10 milligrams and below. Occasional animals did show mild pleocytosis and protein increase. Such animals did not develop any paralysis or weakness when observed sufficiently long. The actual cerebrospinal fluid findings were—(i) seven examinations done on the third day revealed cell counts ranging between 13 to 900. In six the count had been high and only in one it was 13. Proteins were estimated in only three animals and in one the value was 60 milligrams and in the other two 10 milligrams ; (ii) six examinations done on the fifth day showed cell counts ranging between 2 to 132. Only in two cases it had exceeded 20 cells. Protein estimations have been uniformily at a low level of 10 milligrams ; (iii) eleven examinations done on the seventh day revealed cell counts ranging between 1 to 120 cells. Only in three the count had exceeded 20 cells. Proteins were estimated in eight animals and only in one the value was 40 milligrams while the rest were below 15 milligrams per cent. (iv)

Twenty examinations done on the ninth day gave cell counts ranging between 1 to 109 cells. In only one the count was 109 while all the rest had cell counts below 20 cells. Protein values determined in sixteen animals were below 10 milligrams per cent.

It might be mentioned here that the high cell count obtained initially, *e.g.*, on the third day after the inoculation in most animals examined, might be partly due to the effects of the trauma on the brain and the meninges. That this actually is the case can be seen from records of 4 negative animals. Initially there were high cell counts, ranging between 47 and 900 cells and an increase of proteins. The pleocytosis and the protein increase were, however, transient, for on subsequent examinations, the cell counts decreased, so that by the seventh day the cell count came down to below 20 and the protein value to 20 milligrams and below. Microscopic examination of all levels of the brain and the spinal cord of these four animals did not reveal any lesions consistent with poliomyelitis.

DISCUSSION

Commenting upon the changes in the cerebrospinal fluid in monkeys inoculated intranasally, Flexner[1] found that cerebrospinal fluid responded early by two sets of changes—(i) the constant and most pronounced change was an increase in the content of the white cells, chiefly lymphocytes, and (ii) the less constant change was the presence of detectable amount of globulin in the fluid. Of the series of 18 animals presented by Flexner[1] in his paper, symptoms indicative of poliomyelitis are mentioned in only 11, whereas the rest have remained symptom-free. Histological studies, however, are not included in his paper in confirmation of the positive takes in his animals.

In our series of animals inoculated intranasally, and which were subsequently proved to be positive, increase of cells and proteins in the cerebrospinal fluid was consistently observed at a stage when there was often no clinical evidence of the disease except a rise of temperature. Such a consistent increase in cells and proteins has not been observed in the negative animals.

In the animals inoculated successfully by the thalamic route a similar increase of cells and proteins in the cerebrospinal fluid has been noted at about the fifth and the seventh day following the inoculation. We discount the third day changes, as these may be partly due to the operative trauma. The average incubation period for this route of inoculation, in our experience, has been 6 to 7 days by which time the animal manifests at least the minimal detectable clinical evidence of the disease *viz.*, weakness or paralysis of the muscles. In addition, the changes in the cerebrospinal fluid in these animals confirm that the clinical findings are those of the experimental disease, and not brought about by trauma incidental to the operative procedure. Whenever there have been doubtful clinical symptoms and examinations of the cerebrospinal fluid have been negative on the fifth and the seventh day after inoculation, it has invariably been a negative take.

The observations presented in this study indicate the value of repeated examinations of the cerebrospinal fluid in detecting the early positive takes in experimental poliomyelitis.

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DIAGNOSIS OF TUBERCULOSIS

"The diagnosis of tuberculosis remains so woefully imperfect today not because of paucity or inadequacy of method. Method we have in abundance—good method, method sufficient for an extraordinarily high average of proficiency. We have clinical method enough and laboratory method enough for first-class attainments. Where we are lacking is in performance. What is wrong lies almost wholly in the great numbers of practitioners who are too busy or uninterested to secure satisfactory clinical histories; too indolent to use the stethoscope or too unpractised to employ it understandingly; too neglectful to keep at the microscopic examination of specimens, of the tuberculin testing of the skin ; too ready to throw the entire burden of diagnosis on the X-ray. Experience continues to teach that the thoroughly useful methods in the diagnosis of tuberculosis are not the difficult, the complicated, the cumbersome, the recondite ones—the ones employable only by the 'specialist'. It is safe to say that a fourth-year medical student can diagnose 80 per cent, and better, of all *diagnosable* cases of pulmonary tuberculosis through the employment of a few, a very few, simple and well-tried manoeuvres, *if only will use them*............."

—A. K. Krause, quoted by Martin Cummings, American Practitioner and Digest of Treatment 2: 6, 502-504, June 1951.

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SPRINGS ETERNAL

He is the best physician who is the best inspirer of hope.—S. T. Coleridge, Medical World, June 8, 1951.

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BARNUM WAS WRONG

A hundred-and-fifty-two babies are born every minute, making nearly a quarter of a million a day or about about eighty million a year. (World Health Organisation.) (about one fourth the population of India).

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JUDGEMENT BY PHYSICIAN

Knowledge makes the physician, not the name of the school.
—Paracelsus (1493-1541). Medical World, June 1, 1951.

DURATION OF INFECTIVITY OF MONKEY CORD IN LABORATORY POLIO INFECTION †

P. V. Gharpure * and C. S. Swaminathan *

During the course of the work with strains of the virus of poliomyelitis isolated from Bombay[1], the duration of the survival of the virus under conditions available for the preservation of the virus in this laboratory was determined. The infective material, in the form of portions of the spinal cord and the brain stem removed from monkeys sacrificed following successful inoculation with the virus, was preserved in 50 per cent neutral glycerine, and stored in clean glass vials at temperatures ranging from 4°C to 5°C. These were periodically inoculated into rhesus monkeys by various routes in order both to test their infectivity as well as for passage of the virus strains. A strain of the virus isolated from a pool of stools obtained from two human cases of paralytic poliomyelitis was considered as a test strain for the purposes of this report. This strain has been put through seven passages in rhesus monkeys and the material from the original to the seventh passage was available. An attempt has been made here to analyse a number of these inoculations effected with the material of the original first and second monkey passages, particularly, in respect to the duration of storage of the virus-containing material that was used for inoculation.

EXPERIMENTAL

Healthy adult rhesus monkeys were used throughout, as the experimental animals. A 10 per cent suspension of the cord was used as the inoculum. Following inoculation, the animals were observed for clinical features of the disease, and when those developed, they were sacrificed and representative portions of the spinal cord, brain stem, and cerebral hemisphere subjected to microscopic examination.

RESULTS

The incubation period in this series of inoculations ranged from 3 to 9 days. Changes in the cell count and protein content of the cerebrospinal fluid accompanied the clinical manifestations of poliomyelitis, and histological examinations of the central nervous system confirmed the clinical disease. To the date of reporting, it has been found that the virus had survived for a period of 10 months (Table) under the conditions that were available for its preservation. The study of the survival of the virus for longer periods of storage is under investigation.

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† Paper read at the Annual Conference of the Association of Pathologists of India, held at Hyderabad, in November, 1951.

* From the Polio Research Unit of the Indian Council of Medical Research, Pathology School, Grant Medical College, Bombay 8.

TABLE 1.—*Duration of Infectivity of Monkey Cord in Laboratory Polio Infection.*

Virus material tested.		Infectivity tested at intervals of (in months).									
		1	2	3	4	5	6	7	8	9	10
Original M-10		† (7) (IT)	† (6) (IS)			† (7) (IT)					† (10) (IT)
First passage of M-10 strain ..	M-8			† (6) (IT)	† (10) (IS)		† (5) (IT)			† (8) (IT)	
	M-11			† (5) (IT)				† (5) (IT)			† (9) (IT)
	M-39				† (7) (IT)						† (7) (IT)
Second passage of M-10 strain ..	M-15	† (6) (IT)				† (5) (IT)			† (10) (IT)		
	M-23	† (6) (IS)					† (7) (IT)				
	M-36	† (5) (IT)									† (7) (IT)

† Clinically and histologically positive. (IT) Inoculated by the intrathalamic route. (IS) Inoculated by the sciatic route.

( ) The figure in the brackets denotes the number of days for the manifestation of the first clinical symptom of poliomyelitis.

DISCUSSION

The identification of the virus strains as those of *poliomyelitis* has been discussed elsewhere[1]. It has been found that the inoculation of the material from three passages of one strain of the virus has been capable of infecting the susceptible rhesus monkeys after periods of storage ranging upto 10 months. This is similar to the known property of the virus of poliomyelitis which, in common with other neurotropic viruses, has the ability to survive for considerable periods of time in the cold[2].

An analysis of the results that have been considered in this report does not permit of any quantitative evaluation of the effects of storage under the conditions stated, on the infectivity titre of the virus strain. The dose that has been used for each thalamic inoculation has been kept constant within the limits of laboratory error, nevertheless the amount of virus inoculated into each animal is considerably more than what has subsequently been determined to be the minimum infective titre for this strain. To that extent, it is only possible to state that the virus strain has survived for 10 months as determined by its capability to produce clinical and pathological poliomyelitis in the rhesus monkey.

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First Things First

Physicians ought to console their patients even if the signs of impending death seems to be present. For the bodies of men are dependent on their spirits. In treating a patient let your first thought be to strengthen his natural vitality. If you strengthen that, you remove ever so many ills without more ado. If you awaken it, however, by the remedies that you use you always work harm. The patient who consults a great many physicians is likely to have a very confused state of mind. Medical World, 75: Dec. 1951.

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Believe it or not:—According to a report in the New York Times (October 3) workers from Duke University School of Medicine claim to have discovered what they call a universal antidote for poisons the nature of which is not known. It is made up of burned toast, strong tea, and milk of magnesia. The toast is supposed to provide pulverized charcoal to absorb toxic substances, the tannic acid content of the tea to help offset an alkaline poison, and the milk of magnesia to neutralise an acid poison.—B. M. J. 2: 938, 1951.

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Intramuscular injection of a microcrystalline suspension of chloramphenicol is a feasible mode of administration of the drug. In infants weighing from 3 to 12 Kg. adequate blood levels lasting for at least 24 hours may be obtained with a daily injection of 1.0 Gm.—Excerpta Medica, 5 : 1156, September, 1951.

SALMONELLA PARATYPHI C MENINGITIS*

REPORT OF A CASE

B. P. Tribedi †, C. R. Banerjea † and S. K. Sen †.

Meningitis due to various Salmonella organisms has from time to time been recorded but that due to *Salmonella paratyphi C* has seldom been reported. The report of two cases by Beattie, Lawy and Taylor[1] is the only specific reference found in the available issues of the Index Medicus.

Neter[6] in his review of literature relating to meningitis caused by salmonella group of organisms over the last 20 years did not find any reference to a case due to *Salmonella paratypi C*. Henderson[5] also in a review of one hundred and forty cases of Salmonella meningitis from literature did not find any case due to *Salmonella paratyphi C*.

No reference is available of any study or report of any case of meningitis due to Salmonella organisms, not to speak, specifically of *Salmonella paratyphi C*, is available in literature in India. It is for all these reasons the following brief note of a case admitted in the Calcutta Medical College Hospitals who died and whose post mortem examination they held is recorded here.

CASE REPORT

A Hindu female child, aged 3 months, coming from one of the refugee colonies near about Calcutta was admitted to the Medical College Hospitals' Pediatric Department in the evening of 26-8-51 for the following complaints :—(1) Fever—more or less continuous—5 days. (2) Loose motions 3-4 times a day for 5 days, and (3) Convulsions for 4 days. The patient's condition was very bad on the morning of admission.

History revealed no previous serious illness. Birth had been normal and at full term. The diet consisted of breast feeds, milk and barley. No history of contact with tuberculous patients given.

Physical Examination :—The baby appeared acutely ill, dehydrated, marasmic and was having convulsions. The rectal temperature was 101.6° F, pulse was almost imperceptible and respiration hurried. The anterior fontanel was depressed. Skin showed old marks of healed pemphigus, neck exhibited slight rigidity. Tongue was coated and dry and throat showed a little congestion. There was nothing in the ears and no discharge from the nose.

The liver was enlarged 1 1/2 inches below the costal margin. The spleen was not palpable. Heart sounds were feeble and there was nothing abnormal in the lungs, except hurried respiration.

Laboratory Data :—The leucocyte count was 8,200 per c.mm. of blood with 42 per cent neutrophils, 54 per cent lymphocytes and 4 per cent monocytes. No malaria parasites were found.

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* Paper read at the Annual Conference of the Association of Pathologists of India, held at Hyderabad, in November 1951.

† Department of Pathology & Bacteriology, Medical College, Calcutta.

Urine analysis did not reveal anything abnormal.

A lumbar puncture was not done as the condition of the patient was very unsatisfactory.

Five hundred and forty cc. of glucose saline was given immediately by the open method and the patient was put on penicillin, *etc.*

Late at night the temperature shot up to 106° F and the patient died the next morning.

Autopsy Examination :—An autopsy examination was held on 28-8-51.

Development was average, nourishment was poor. There was no sign of edema anywhere. There were healed scars of pemphigus all over the body.

Internally, there was general pallor of the lungs with multiple petechial subpleural hemorrhages. The liver was slightly enlarged and the cut-surface was pale and fatty in appearance. The adrenals showed multiple hemorrhagic areas of different sizes—pin point to sago grain.

Nothing abnormal was found in the intestines.

On cutting open the dura the surface of the brain was found covered with a thick slightly greenish pus over the frontal, parietal and part of the occipital lobe. The pons, medulla and the spinal cord, specially in the lower thoracic and lumbar regions were all bathed in thin pus.

The other organs appeared more or less normal.

The heart's blood culture was sterile but on culturing the pus over the meninges a pure growth of a gram negative motile, non-lactose fermenting bacillus was isolated which was identified as *Salmonella paratyphi C*, on the basis of the following biochemical and serological reactions :—

Glucose	Acid and gas.
Lactose	No fermentation.
Maltose	Acid and gas.
Dulcitol	Acid and gas.
Mannitol	Acid and gas.
Arabinose	Acid and gas.
Saccharose	No fermentation.
Xylose	Acid and gas.
Indol production	Negative.
H_2S. production	Negative.

When examined serologically the organism readily agglutinated with our stock high titre *Salmonella paratyphi C* antisera.

DISCUSSION

Among the infections due to salmonella organisms that due to *S. paratyphi C* has been regarded as rather uncommon and the literature in India regarding the incidence of this infection is also very scanty. Wasti[9] published 9 cases of *S. paratyphi C* infection causing enteric fever and De, Tribedi and De[4] have recorded 15 cases of enteric fever due to *S. paratyphi C* infection as found out from blood cultures from Calcutta. From 1946 to the present day, apart from the meningitis case now reported, there has been one case only of *Salmonella paratyphi C* isolated from blood cultures in our laboratory, which fact only indicate the rarity of the infection in this part of the country.

In Beattie, Lawy and Taylors'[1] two cases, the organisms were isolated from the cerebrospinal fluid removed by the lumbar puncture. In our case lumbar puncture was not possible as the condition of the child was very unsatisfactory.

Salmonella paratyphi C has been stated to be prone to produce lesions of a septic type (Topley and Wilson[8]) and clinically Bornstein[2] has also placed it in the septicemic group of organisms. Naturally, one may expect this organism to produce meningitis with a relatively greater frequency than any other organisms of the *Salmonella* group. The fact that such cases are uncommon may be easily attributed to the rarity of the incidence of *S. paratyphi C* infection. The presence of multiple petechae in lungs and adrenals of the reported cases only indicate the septicemic nature of the organisms. But the sterile heart's blood culture points to the tendency of localisation on the part of the organisms.

In their study of the incidence of meningitis in early infancy, Cooke and Bell[3] suggested a high permeability of the intestinal mucosa and low resistance to these organisms and a tendency to localisation anywhere in the body.

Unlike the usual finding of basal collection of pus, in our case it was more on the vertex.

In the case reported here, diarrhea has been an important feature and Ramon Guerra and his associates[7], in a review of 59 cases of *Salmonella* meningitis, noted the tendency of the disease to affect infants and children and that it runs a fatal course with diarrhea as a prominent symptom.

In accounting for the occurrence of *Salmonella* meningitis both Neter[6] and Henderson[5] emphasized the importance of lowered tissue resistance. The devitalized condition of the child in the refugee camp—marasmic as she was, paved the way for the easy infection.

In this connection it may be relevant to note here that *Salmonella paratyphi C* infection exists endemically in British Guiana, Indonesia, Malaya and Eastern Europe (Manson Bahr[10]). De, Tribedi and De[4] pointed out a steady increase in the incidence of *S. paratyphi C* infection in this country since 1942 and a suggestion has also been made regarding the possible relationship of carriers among the Burma evacuees. Now in our case no definite relationship of contact with persons coming from far Eastern countries could be traced.

ACKNOWLEDGMENT

We wish to thank Dr. D. C. Chakravarti, Principal-Superintendent, Medical College and Hospitals, Calcutta, for kindly permitting us to use the hospital records and Dr. K. C. Chaudhuri, Physician-in-charge, Pediatric Department, Medical College Hospital, for kindly allowing us to report the case.

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Believe it or not:—The study of neurosis in animals can help research in human medicine in two ways: emotions displayed in simplified form by animals may help to reveal vital underlying human feelings often masked by social conventions, and secondly, controlled experimental work on animals yields much information which, althought it cannot be directly applied to humans, shed light on many problems. Anxiety neurosis in cows is often seen, the cow refusing to part with her milk in the presence of a stranger, for instance. Horses too, are prone to neuroses, and are specially susceptible to the temperament of the human beings they come in contact with a neurotic rider can reduce a normally calm horse to a state of nervous tension in a few minutes, often making it quite unmanageable. Goats frequently become neurotic if they are made to do something they do not want to do, simulating epileptic fits which pass off immediately they are allowed their own way. Possible causes are threefold; heredity is probably the strongest. Inbreeding in dogs has led to an increase in hysteria and instability, and it is significant that dogs trained to lead the blind are now mainly first crosses form Labradors and Alsatians, and no longer pure-bred Alsatians. Environment also plays some part in the production of neurosis, and this is mainly the effect of the humans with whom they are in contact.

In every species it is the most intelligent animals that display neurotic symptoms. Since temperament is inherited to a great extent, no animal known to be neurotic should be allowed to breed, but this ideal will probably never be achieved because, for example, if a cow is a high milk-yielder it is very unlikely that her owner will not breed from her, regardless of temperament.—B. M. J. 2: 961, 1951.

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Why diet the diabetic?

The author does not think it necessary to prescribe a diet for diabetic patients unless the patient is overweight. He gives details of the age, insulin dosage and causes of admission to hospital, of 191 patients, who lived in New South Wales, Australia, and who had been observed between 1946 and 1950. The patients are stated to be well. The results of this experiment should be repeated in another 20 year's time to give some idea of the benefit and complications which result.—(Quoted from Excerpta Medica, 7: 1268, 1951).

HYDATID DISEASE OF THE LUNGS *

A case report

B. P. Trivedi, † **B. Chowdhury** † and **D. Barua** †

Like many other diseases in India, the reported cases of hydatid disease bear very little relation to the real incidence of the infection. Reference has been made in the past by many writers to the relative rarity of hydatid infection in India, but Maplestone[3], after reviewing the recorded cases of hydatid infection, suggested that hydatid disease is commoner in India than the reported cases seem to indicate. To explain the comparative rarity, various reasons have been advanced. Though the dog is not such a close and popular pet in India as in Europe or Australia. dog's excreta containing eggs of *T. echinococcus* has an equal, if not, a greater chance of infecting men by contaminated water, food. vegetables either directly or through the agency of flies.

Maplestone[3] after dissection of 100 dogs found adult *T. echinococcus* in the intestine of only 2 dogs whereas Dews[2] found almost 100 per cent infestation in Melbourne, Australia. The dogs dissected by Maplestone were from the city of Calcutta and he thought that the figure would be probably higher in rural areas where the chance of infection is definitely higher. Later on, Maplestone and Bhaduri[4] found the incidence of *E. granulosus* in 18 per cent of pariah dogs in Calcutta. Sami[6] drew attention to the relatively higher incidence in a rural area in the Punjab.

However, on the medical literature available, it is difficult to arrive at an estimate of incidence of this disease in India. In last 31 years, 2,989 autopsies have been performed in the Pathology Department, Medical College, Calcutta and this is the only case of hydatid disease that has been met with. From the register of various materials examined in this department from various wings of the Medical College Hospitals. records of 11 hydatid cysts of different organs are available. Thus altogether there are records of 12 cases in this department, of these 4 were in the liver, 2 in the lungs, 3 in the spleen, 1 each in the kidney, breast and peritoneum.

Going through published records of hydatid disease in India, it is found that only three cases of hydatid disease of the lungs have been published by Tulsidas and Prithichand[7], Ukil and Ganguli[8] and Chopra, Pasricha and Lal[1]. All these cases were diagnosed and treated, during life.

CASE REPORT

A hindu male, aged 60 years, was a cultivator by profession and was an inhabitant of a village in West Bengal. He was admitted in Medical College Hospital with symptoms of acute on chronic intestinal obstruction *viz.*, constipation with occasional passage of flatus and feces for 18 days, absolute constipation for 6 days, vomiting several times a day and hiccough for 15 days.

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* Paper read at the Annual Conference of the Association of Pathologists of India, at Hyderabad, in November 1951.

† Department of Pathology, Medical College, Calcutta.

On examination, general condition was found to be very low. He was very anemic and his abdomen was distended all over ; peristaltic sounds were present. No abnormality was detected on examination of the heart and lungs. On rectal examination a hard fixed mass was found around the pelvirectal junction and blood was found on the examining fingers. He was operated on the same day after resuscitation ; on opening the abdomen an inoperable hard growth was found occupying the pelvis. The surgeon had to be satisfied with a left inguinal colostomy after relieving the distension, and the wound was closed. The general condition of the patient became worse, extremities became cold and clammy and the patient died 5 1/2 hours after operation. An autopsy was performed and the relevant findings were :—

1. A hard mass arising from the rectum causing much narrowing of the lumen of the rectum. Histological examination of the growth proved to be an adenocarcinoma.

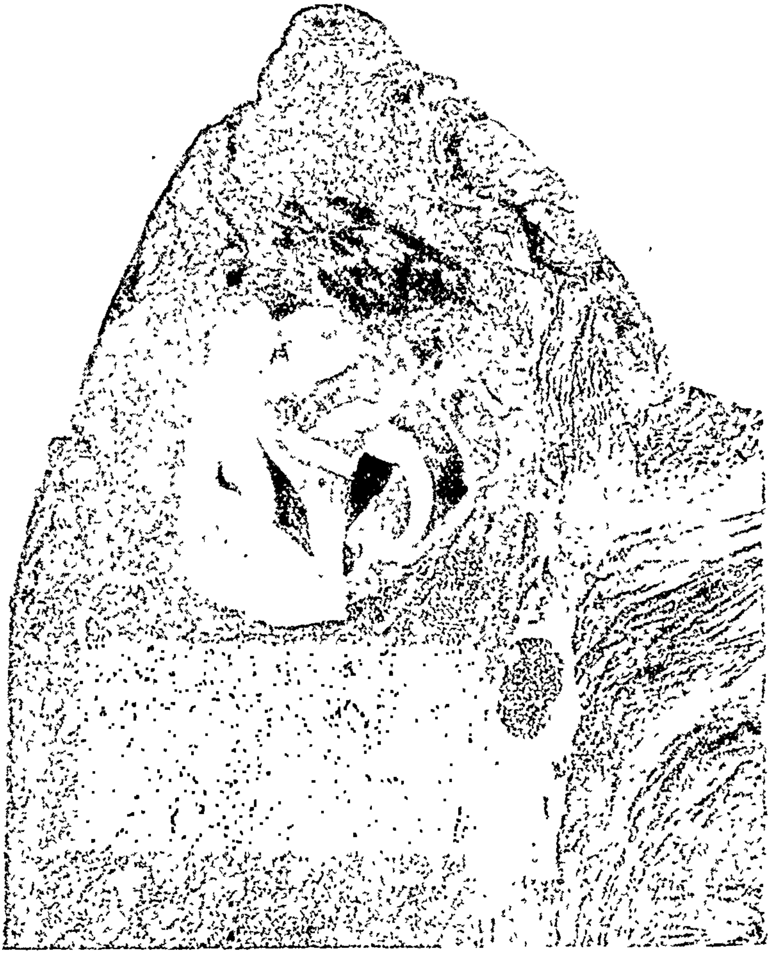

Fig. 1.—Photograph showing hydatid cyst in the left lung.

2. An unilocular type of hydatid cyst was found in the upper lobe of the left lung in the subapical zone. It was about 2″ × 1 1/2″ in size. Inside the cyst there

were daughter cysts. Fluid from the cysts on microscopical examination showed hooklets, scolices and broodcapsules.

3. 6 ozs. of straw coloured fluid in the left pleural cavity. The fluid did not show any scolex or hooklets on microscopical examination.
4. 2 ozs. of straw coloured fluid in the right pleural cavity
5. Atheromatous patches in the commencement of the aorta and the commissures of the aortic valves were adherent.
6. Pulmonary edema was present in both lungs.

DISCUSSION

This case was free from any symptom and this may be explained by the fact that the cyst is a small one and it could not cause much of pulmonary fibrosis or bronchial obstruction nor was it big enough to rupture into the pleural cavity or bronchi or any neighbouring structure. The presence of a single cyst in the upper lobe of the lung without involving the liver provides an example of the embryo reaching the lung through the pulmonary artery, gaining access to the general blood stream either by-passing the liver or through the liver.

One case of hydatid cyst in 2,989 autopsies surely tends to show a low incidence, but the hospital register tells a different tale. 5.6 to 16.8 per cent of all hydatid disease in different countries occur in the lung (Price[5]). Maplestone[3] recorded 5 per cent of all hydatid disease involving the lung in India in a series of only 20 cases.

The hydatid cysts live in complete harmony with the hosts and produce very little symptoms until very late and have almost no characteristic clinical features. Most of the cases of hydatid disease are diagnosed only on the operation table and on demonstration of scolex and hooklets in the contents on microscopical examination. This case is considered worth recording as it is felt that because of the paucity of recorded cases of this disease in India, hydatid cyst is not given its due consideration as a possibility in a probable case.

ACKNOWLEDGMENT

Our grateful thanks are due to Dr. D. C. Chakravarti M. B., F.R.C.S., Superintendent, Medical College Hospitals, Calcutta and to Dr. S. M. Ghosh M.B., F.R.C.S., the Surgeon, under whom the case was admitted, for their kind permission to utilise the hospital records.

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VITAMINS IN HONEY

The attempt to learn whether honey contained vitamins began in 1918, with a number of investigators claiming that honey had no vitamin content. According to the analyses of three honeys, done in Germany in 1924 by Scheunert, Schieblich and Schawnebeck, no vitamins were found to be present. But more recent analyses, notably those done in 1942 and 1943 at the University of Minnesota and the University of Wisconsin have proven this to be incorrect.

Honey does contain vitamins in highly variable amounts. These have been listed by Milum as follows :

Vitamin A (minute and insignificant amounts).
Vitamin B-complex (several involved in carbohydrate and amino acid metabolism).
B_1 Thiamine (antineuritic factor, antiberiberi).
B_2 Riboflavin or vitamin G (growth and metabolism).
B_6 Pyridoxine (growth and amino acid metabolism).
Biotin (nutrition, some relation to dermatitis).
Folic acid (growth and nutrition).
Nicotinic acid (cure and prevention of pellagra).
Pantothenic acid (growth and metabolism).
Vitamin C-Ascorbic acid (antiscorbutic factor, cure and prevention of scurvy).

The amounts of vitamins are small but we must not lose sight of the fact that they are directly absorbed into the blood stream with the predigested sugar. This direct absorption of honey accounts for the remarkable energy response following its ingestion. There is no waste of vitamins; whatever vitamins the honey contains are completely utilized.

It behoves us, therefore, to consider seriously the use of honey as a natural source of vitamins, especially since it is becoming increasingly evident that with the advent of synthetic vitamins we are overdosing ourselves with vitamins in general, and untoward reactions of vitamin overdosage are being reported in the literature.

—Medical Times. (Quoted from Medical World, June 1, 1951.)

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Aphorism of the Month : An observant parent's evidence may be disproved but should never be ignored. Lancet, London.

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A "universal medicine" for all ailments is recommended to doctors by Dr. W. W. Bauer, director of the American Medical Association's Bureau of Health Education.

To mix it, he says, "take three parts of the kindliness, personal interest and knowledge of human nature of the old-fashioned horse-and-buggy doctor, one part of the spirit of service and self-sacrifice, and apply liberally to the human factor in every illness."

PULMONARY ACTINOMYCOSIS *

B. P. Trivedi † and **S. K. Sarkar.** †

Although actinomycosis is not a common disease, it offers problems which often baffle the clinicians.

According to Topley and Wilson, the percentage of thoracic actinomycosis is 14.3. Of these all were not pulmonary actinomycosis. The total number of cases of actinomycosis reported in Medical College, Bengal, were 32. of which none was pulmonary actinomycosis. We agree with Butterfield in observing that the number of the interesting cases reported under the names of pseudotuberculosis cladothrichica, pseudo tuberculosis streptothrichica, actinomycosis atypica pseudo tuberculosa. together with the attempts of Gasperini, Levy and his pupils. Lachner, Sandoval and Nenkirch, to establish the botanical position of the so-called Streptothrices on morphological and biological grounds, justifies the report of another similar case.

CASE REPORT

History and Clinical Findings :—A Hindu male, aged 40 years, was admitted in M.L.S ward, Medical College Hospitals on 30-12-49.

Date and hours of death : 9-10 a.m. on 23-1-50.

Date and hours of autopsy : 2 p.m. on 25-1-50.

The patient was admitted with the following complaints :—

(a) Tenderness and swelling on the left side of the back (3 months), (b) gradual emaciation (4 months).

On examination :—His general condition was poor, with marked emaciation.

There was slight anemia, glossitis being present. There was tenderness and a diffuse swelling on the right side at the renal angle. The abdomen was soft, with tenderness in the right lumbar and hypochondriac regions. The liver and spleen were not palpable. Moist sounds were heard at bases of both lungs. No abnormality was detected in the cardiovascular system.

Note :—1-1-50—Blood and mucus passed in the stool 8 to 10 times a day.

E. histolytica (vegetative form) found on examination of the stool.

2-1-50—Twenty oz. of thick, viscid, mucoid, yellowish-red pus was aspirated from right hypochondriac region.

The sputum was clear.

20-1-50—The patient's condition became worse. Looseness of bowel increased and he died on 23-1-50 of cachexia at 9-10 a.m.

Past history:—He had been admitted in the Medical College Hospitals on 23-9-49 as a case of pericolic abscess and discharged on 3-11-49.

Clinical diagnosis :—A malignant growth of the cecum with a paracolic abscess.

Autopsy Findings :—The body was of a male, of fair development but of poor nutrition, rigor mortis having passed ; no lividity, and no edema. The pupils were dilated—the tongue, raw—teeth and gums, unhealthy—the skin, dry and scaly.

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* Paper read at the Annual Conference of the Association of Pathologists of India, held at Hyderabad, in November, 1951.

† Department of Pathology and Bacteriology, Medical College, Calcutta.

Peritoneal cavity :—The appendix was 4.5 cm. long, paracecal. Mesenteric lymph nodes were enlarged with no caseation seen.

Pleural cavities :—In the left, 2 oz. of straw coloured fluid were present. In the right there were very firm adhesions medially and lower down (at base) ; soft adhesions at apex and laterally. Pericardial cavity :—Several milk spots were seen on the anterior aspect.

Heart :—Wt. 170 Gm. T.V.—IIcm. P. V.—6 cm. M. V.—9.5 cm. A. V.—6.5 cm. R. V. wall—0,5 cm. L. V. wall—1.5 cm. Muscles—slightly pale.

Lungs :—Right—on trying to separate the adhesions medially, thick, yellowish pus came out profusely. Pus points were seen in smaller branches of the bronchi. Many small tubercle like foci were seen scattered all over the lungs especially over lower lobe. Some of the foci were firm and solid. The lobes were firm and consolidated. Left—a similar picture as on the right one except that the lesions were less marked and there were no adhesions.

Tracheo-bronchial lymph glands were enlarged. No caseation was seen.

Liver :—Enlarged and decomposed. Wt.—1,125 Gm.

Gall-bladder :—Thickened, contained thick, greenish bile.

Spleen :—Firm, chocolate coloured, with a prominent reticulum.

Kidney :—Right—Wt. 100 Gm. The medulla was congested, and the capsule stripped easily. Left—The same as the right.

Skeletal Muscles :—Thick yellowish pus in a profuse quantity in between the psoas muscles and the quadratus lumborum on the right side. The collection extended from the iliac bone on right upto the adhesions in the thoracic carity. The back muscles showed a collection of pus on the right side.

Bones and joints :—Thoraco—lumbar group of vertebrae appeared necrotic and contained pus, the column of pus communicating with the pus collected in the skeletal muscles. The inter-vertebral discs were intact.

Bone-marrow :—An erythroblastic reaction was seen.

Wounds and scars :—A needle mark in the right hypochondriac region was noted laterally.

A swelling of the size of an orange was detected on the right paravetebral region (10th-11th dorsal spine).

Microscopic Findings :—

Liver :—No structural abnormality was noted except a fine distribution of pigments (malarial) in the Kupffer cells.

Spleen :—The trabeculae were prominent. There was an increase in connective tissue. The splenic sinuses were congested and contained pigment-laden (malarial) cells.

Heart :—Chronic inflammatory changes were present in the pericardium, degeneration (post-mortem) in the muscles.

Suprarenals :—Degenerative changes seen.

Kidney :—Degenerative changes in tubules and glomeruli.

Gall-bladder :—Chronic cholecystitic changes were seen. (Thickened muscle coat and submucosa and atrophy of the mucosa).

Diaphragm :—Muscle showed actinomycotic granulation tissue with much fibrosis. Pus from paravertebral region showed actinomycotic granulation tissue.

Bone :—Actinomycotic granulation tissue seen together with Actinomyces. Osteo-porosis was seen.

Lymph nodes :—Only an excess of carbon particles were seen. No actinomyces were seen.

Lung :—The alveoli were affected in patches. Those affected were filled with a dense collection of polymorphonuclear neutrophils as well as with some mononuclear

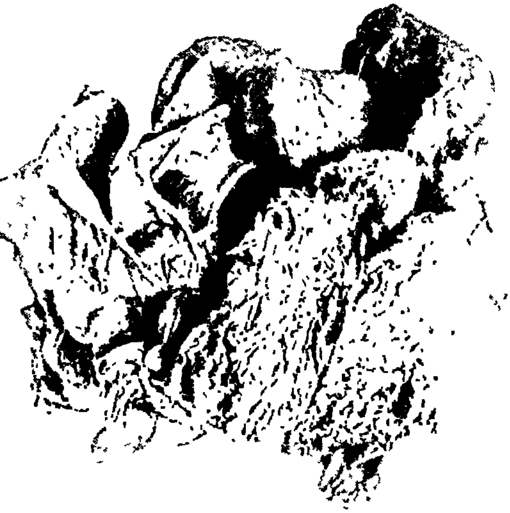

Fig. 1.—Plate showing a lung specimen.

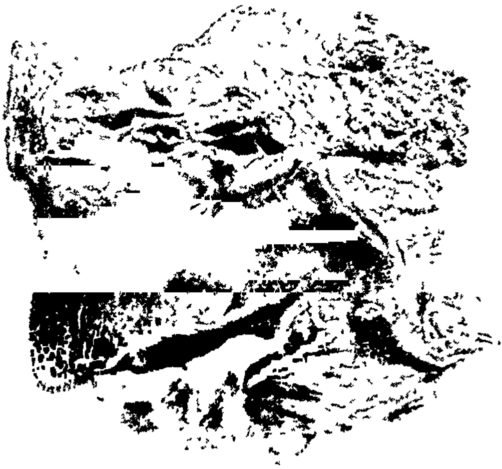

Fig. 2.—Plate showing a lung specimen.

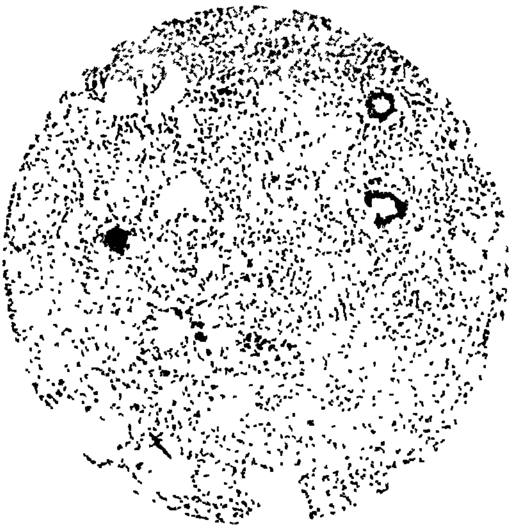

Fig. 3.—Photomicrograph showing actinomyces.

cells, lymphocytes and plasma-cells. In other alveoli, the cellular accumulation was less prominent and some granular or homogenous albuminous material filled them in turn. Other alveoli were normal or emphysematous. Actinomyces were present in some of the affected zones.

Bronchi and bronchioles :—There was infiltration of the walls with leucocytes specially polymorphonuclear neutrophils as well as fibrinous material, desquamation of epithelium and filling of the lumen with an exudate of fibrin and leucocytes. Actinomyces were seen in the inflammed bronchioles.

Blood Vessels :—Alveolar capillaries were engorged and packed with red blood cells together with a relative excess of polymorphonuclear neutrophils. Hyaline thrombi occluded some capillaries in the intensely inflammed areas. The medium and large calibered vessels had an adventitial mantle of small mononuclear cells and contained an excess of red blood cells, polymorphonuclear neutrophils and small amount of fibrin. No actinomyces were seen.

HISTORICAL

In the dawn of our knowledge of the disease, the names of Langebeck, Davine, Robin, Rivolta and Porroncito demand special mention. Most of the early works on the subject were carried on the diseases as it occured in animals—the lumpy jaw of cattle. Bollinger as far back as 1877 described the fungoid nature of the disease and his colleague Harz christened the organism "actinomyces and the disease actinomycosis". Israel was also at that time an independent traveller in quest of knowledge about this organism. Not until 1879, was the causative role of actinomyces in human diseases established, and Ponfick was credited with this honour. The clinical studies on the subject made incredible progress but the difficulty in cultivation as well as absence of early definite results in animal inoculations created a lag phase in the sphere of bacteriological study. The stamping of the pathogen as an anerobe or an aerobe initiated the Bostroem—Wolff dispute which took years to settle down, if it can be said to be settled yet. Then came forward the famous Carl Naeslund with his mastery publication which served to dispel much of our ignorance, and to further knowledge. In his verdict neither Bostroem nor Wolff could have it all his own way—each won and each lost. The anerobic organism was already credited with the role of a pathogen. Now came the turn of the aerobic counter part. Biggert in 1934 and Trivedi in 1939 asserted with conclusive evidences the role of the aerobic type as pathogens. In 1882, Pflug described a miliary pseudotuberculosis due to actinomyces. Bostroem reported a case which on autopsy revealed pneumothorax, pleurisy and pulmonary cavitation due to actinomyces. Orth depicted abscess formation in the lungs, involvement of pleura, vertebral column, pericardium, diaphragm and peritoneum due to actinomyces. Schabad found in his case, in addition to the pulmonary cavity, caries of the adjacent ribs and intermuscular abscess. Butterfield in 1905 put forward a masterly description of a case of pulmonary actinomycosis with a unique histopathological description. Biggert in 1934 described a fatal case of pulmonary actinomycosis due to aerobic actinomyces. Sen described a case of pulmonary actinomycosis diagnosed clinically and substantiated by sputum examination.

DISCUSSION

The thoracic actinomycosis (roughly one in every seven cases) manifests itself in two forms, the mediastinal and the pulmonary, though one may merge into another. The mediastinal variety can be a primary one penetrating through the esophagus and affects mainly the posterior mediastinum. It may be secondary, tracking down from a cervical focus or travelling up from a retroperitoneal or hepatic lesion and involving in either case the superior and posterior mediastinum. Due to anatomical apposition of the superior and posterior mediastinum, the pleura runs a great chance of involvement and in turn hands down the process to the lung. In the case under report as, no mediastinal lesion was detectable, the idea of pulmonary involvement from a mediastinal source can be discarded. The idea of metastatic affection of the lungs can also be discarded due to the absence of any detectable primary source. This leaves us with the primary involvement of the lungs and this in turn is more common. In majority of these cases the infection is by inhalation of fungal elements into the lungs, the aspiration of liquid material or a carious tooth being a rarity. Contrary to the demonstration by Israel, Turner Warwick and others, we did not find anything pointing to carious tooth aspiration. Innumerable opportunities do exist for infection to take place by inhalation of dust particles contaminated with actinomyces—the aerobic type of which abound in the soil of our agricultural country.

According to Topley and Wilson, the first lesion is in the peribronchial lymph node which in our case was not so. Cope describes the mode of spread in lung as follows : With the lodgement of the organism in the lung parenchyma, a local consolidation starts and despite a great defensive reaction the lesion spreads steadily and slowly by a process of continuity and contінguity. Thus a major part of the lung is involved. Later on, caseation, central softening and even cavitation may occur. The gravity theory has been postulated to explain the greater frequency of lesions in lower lobes. In the case under report, the degree of involvement was most marked in lower parts of the lower lobes.

As the process reaches the visceral pleura, an outpouring of an effusion in the pleural cavity occurs. At first clear, it soon becomes purulent and in cases of small effusions, pleural adhesions soon follow. Later, there is infiltration of the thoracic wall with inflammatory cells and formation of a pointing empyema. The gravity theory attempts to explain the usual pointing of empyema necessitatis at the level of the bottom of the pleural cavity, opposite the diaphragmatic attachment.

In the case under report, there was an orange sized swelling on the right paravertebral lower dorsal region (10th-11th dorsal spine).

Extension by continuity may carry the fungus far and wide—into the pericardium, myocardium, the meninges through the intervertebral foramina, to the hip or buttock via the subcutaneous tissue and last but not the least, the rare downward tracking behind the diaphragm. The case under report showed this rare downward tracking behind the diaphragm and through the psoas muscle and the quadratus lumborum as far down as the iliac bone on the right side. Blood dissemination especially to the brain is said to occur but we did not find any such lesion.

Though Schwarz, Keynes and Bates, Bevan and Rauber have demonstrated the actinomyces in lymph glands, the lymphatic system is said to be more immune to this disease. The fanciful hypothesis of actinomyces being too big to sail through the small lymphatics was propagated at one time to explain this relative resistance of the lymphatic system. But it could not stand the severe critical tests and the demonstration of the living fungal elements within a leucocyte, which ended this view. In the case under report, despite a search in several sections of the lymph nodes failed to exhibit any actinomyces.

. Affection of bones and joints by actinomyces, needs consideration under three headings viz., primary infection of the bone, metastatic foci, and involvement by neighbouring disease.

A survey of the case under report, dispenses with the primary infection as well as metastatic foci. In this case the vertebral bodies were affected by the neighbouring disease—the adjacent accumulation of pus in the muscle layers. The psoas muscle by virtue of its intimate relation with the vertebral bodies, especially the lumbar group, paved the path of the disease to reach and erode the vertebral column. The involvement of the vertebral bodies is said to manifest itself in two co-existing forms—osteoporosis in the zone of maximum intensity of lesion and osteoplastic reaction in areas of less irritation. The case under report exhibited actinomycotic granulation tissue with osteoporosis but showed no definite osteoplastic reaction.

The peritoneum is said to be resistant to infection in contra-distinction to the pleura. Several cases have been reported where large masses of retroperitoneal tissue bulged into the peritoneal cavities without involvement of the peritoneum. Though these masses were aspirated through the peritoneal cavity, there were no actinomycotic lesions of the peritoneum. In the case under report, there was a huge retroperitoneal collection which was aspirated per abdomen in life and yet exhibited no peritoneal change, ante-mortem or post-mortem.

SUMMARY

The actinomycotic lesion started in the lungs (markedly in the

right one), involved the pleura on the right side and coursed its way behind the diaphragm in between the psoas and the quadratus lumborum on the right side as far down as the right iliac bone. Lying adjacent to the vertebral bodies, the process did not spare the vertebrae, the contagious surface of these bones being eroded. Confirmatory to customary findings, the tracheo-bronchial lymph-glands and the peritoneum demonstrated an explicable resistance.

The interesting feature of this case is that such a gross involvement of the lung escaped the notice of the clinician, the only observations that he found was a few rales at the bases which naturally did not draw much attention. It shows clearly how a case of pulmonary actinomycosis could be mistaken as paracolic abscess and a neoplasm which naturally calls for autopsies and more autopsies.

ACKNOWLEDGMENT

We convey our sincere thanks to the Superintendent, Medical College Hospitals, Calcutta, and the Surgeon-in-Charge for allowing us to use Hospital records.

The belief that the more unpleasant the medicine the more effective it is, seems to be given up gradually. At present the medicaments are attractively flavoured and coloured by almost all pharmaceutical concerns. No doubt, the medicines should be as pleasant as possible for children, but it should be well remembered that generally the potent chemotherapeutic and pharmacological preparations which have a relatively small margin of safety between the therapeutic and toxic doses for the children or infants are made thus attractive. It is therefore incumbent upon every practitioner to bear in mind the following risks while prescribing such preparations. A careless mother may give an overdose ; and inquisitive child may discover the pleasantly flavoured liquid or attractively coloured pills and swallow an undesirably large dose: or the practitioner on whom the final responsibility falls morally, may not emphasize strongly enough to the mother or nurse that the prescribed dose should not be exceeded under any circumstances.

The drugs prepared thus are sulphonamides, antihistaminics, codein, phenobarbitone, amidone, myanesin, pentamethonium, stilbestrol, dextro-amphetamine, and inorganic iron salts to be used as hematinics. The only way to prevent these accidents is for doctors to prescribe such preparations only when they are satisfied that they will be given under careful supervision, whether in the home or hospital. If there are any doubts whatsoever a plain tablet or mixture only should be ordered.

SWEET AND DANGEROUS, ANNOTATIONS: B.M.J., 2: 226, 1951.

FURTHER OBSERVATIONS ON HELMINTHIC ANTIGENS [*]

P. V. Gharpure [‡]

I placed some aspects of this question last year before the First Annual Meeting of the Indian Association of Pathologists. During the course of several years' work, I have reported isolated observations relating to biological features of the *Ascaris.* While examining the fluids in which the worms lived in the laboratory I looked out for antigenic substances and it was last year that I reported positive findings *in vitro* with the use of what I considered as an antigen.[†] I have carried out further studies *in vitro* to confirm my previous findings with fresh batches of the antigen and fresh human sera collected in the autopsy room. The sera in the autopsy room were collected during a period of six months (October 1950 to March 1951). The total number of samples of sera collected was 23. Nine of these were found to be unsuitable for study and 14 were actually tested. The antigen was prepared in the manner already described.[†] Sera were preserved by the addition of 1 : 2,000 dilution of merthiolate. The addition of this chemical has not interfered with the reaction. The technique of the test has been kept unchanged and I record again that in all sera from bodies containing *Ascaris* the test was positive in titres upto 1 : 320. In the positive autopsies the number of *Ascaris* has been small (1 to 3). It is, therefore, interesting to note that the higher titre is irrespective of the small number of worms —or, in other words, there is no quantitative relationship between the titre and the number of worms.

Further studies were carried out by inoculating this presumptive antigenic substance in rabbits. A pooled fluid was used and the antigen prepared practically on the same line as described before.[†] The fluid was reconstituted, the resultant being ten times concentrated as compared with the original fluid, having a protein concentration of about 50 mg. per cent.

Two healthy full grown male rabbits were injected in the following manner :—

Date of Inoculation.	Quantity Inoculated. in cc.	Route of Inoculation.
10-7-1951	0.5	Intravenous.
12-7-1951	1.0	Intravenous.
16-7-1951	1.5	Intravenous.
21-7-1951	2.0	Intravenous.

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[*] Paper read at the Annual Conference of the Association of Pathologists of India at Hyderabad, in November, 1951.

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[†] Gharpure P. V.: Helminthic Antigens, Indian Journal of Medical Sciences, 5 : 329-331, 1951.

Sera were collected from these animals as follows :—

Date of bleeding.	Amount of blood collected (in cc.).
25-7-1951	5.0
30-8-1951	5.0
11-9-1951	5.0
20-10-1951	5.0

All these sera have now been tested and there is complete absence of antibody formation upto about 100 days from the last inoculation. The only positive tests were with neat serum kept for 4 hours at 37° C and read after storage in the refrigerator overnight (about 16 hours). This finding is hardly significant.

It would, therefore, be correct to conclude that the substance (or the substances) elaborated by the *Ascaris*, *in vitro*, is a partial antigen.

VOMITING AFTER MORPHIA

Morphine causes nausea in 3 per cent and vomiting in 2.6 per cent when administered to recumbent persons, but when given in similar dosage to ambulant people causes nausea in 40 per cent and vomiting in 16 per cent. It is suggested that morphine sensitises the vomiting centre and that the vestibular activity which accompanies bodily movement causes further stimulation of this centre. When the vestibular apparatus of 14 people was stimulated by spinning them around or syringing one ear with cold water after an injection of morphine, nausea was induced in 10 and vomiting in 6. The anti-histamine drug, "dramamine," prevents nausea and vomiting evoked by vestibular stimulation after morphine. Other anti-histamine drugs could be expected to have the same effect. According to the Lancet (1951) morphine should preferably not be given to ambulant patients.—Précis Medical World, 74: 493, 1951.

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THE IMPORTANCE OF CONTROLS

A celebrated doctor said one day in my presence, "In detracting from the art to which I am indebted for so much wealth and so many clients, I know that I lay myself before everything else. I believe and frankly say and maintain that if a hundred or a thousand people, all of the same age, of the same constitution and habits, were seized suddenly by the same illness, and one half of them were to place themselves under the care of doctors, such as they are in our time, whilst the other half entrusted themselves to Nature and to their own discretion, I have not the slightest doubt that there would be more cases of death among the former, and more cases of recovery among the latter."

Another doctor, even more famous and learned, with whom one day I had a confidential talk, candidly and prudently answered my question why he did not abstain from the food he forbade others, by saying, "My friend, if a doctor did himself what he advises others to do or bade them do the same as he does, he would either suffer in health or estate."—Petrarch, Medical World, June 8, 1951.

UNUSUAL TYPE OF VASCULAR MALFORMATION AS A CASE OF FIBRO-CONGESTIVE SPLENOMEGALY *

B. K. Aikat, ‡ and K. D. Sharma †

The old title of "Splenic Anemia", first introduced by Gretsel in 1866, included a variety of conditions of which the most frequent was "Banti's disease."

Banti[1] described a type of splenomegaly which was not associated with the usual well recognised causes of splenic enlargement and described the clinical and histological criteria, which are too well known to be repeated.

Eppinger[3] in 1920, used the term, "hepato-lienal fibrosis", to denote the essential pathological lesions. It was in 1924 when Durr[2] suggested that the changes in the spleen were similar to those found in hepatic cirrhosis. Banti's original concept that the splenomegaly is precursor of cirrhosis has now been abandoned and the changes in the spleen which he regarded as inflammatory, are without any doubt, the result of congestion. Modern investigations, (Larrabee[6], Mc Michael[8] Rousselot[9], and Thomson), have conclusively proved, that the classical histological features of the disease—the dilated sinusoids with thickened collagenous walls, periarterial hemorrhages and siderotic nodules and the periarterial fibrosis and elastosis are the expressions of heightened pressure in the portal circulation. Portal cirrhosis, thrombosis of the portal or splenic vein and fibrosis around the smaller intrahepatic branches of the portal vein, are some of the well recognised causes of portal hypertension which have been associated with this disease. Such demonstrable causes of portal hypertension, do not however, account for all cases of "fibro-congestive splenomegaly." In 40 per cent of the cases, no obvious cause of portal obstruction can be demonstrated (Rousselot[9]), and he suggested that a variation in the vascular pattern may cause similar effects and that congenital abnormalities may account for some of the cases of "congestive splenomegaly" occurring especially in childhood. Cavernomatous malformations of the splenic and the extra-hepatic branches of the portal veins, angiomatous condition of the splenic vein at the hilum of the spleen are the different types of vascular abnormalities which have been described in the pathology of fibro-congestive splenomegaly. I have been suggested that such cavernomatous transformations appeared to follow thrombosis of the portal or splenic veins (Kemperer[5]). The present

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* Paper read at the Annual Conference of the Association of Pathologists of India, held at Hyderabad, in November, 1951.

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case illustrates a distinctive type of malformation affecting the smaller intrahepatic branches of the portal vein associated with similar malformations in some other organs.

CASE REPORT

Clinical History :—The patient, a boy aged 15 years, was admitted to the Medical College Hospital, Nagpur, complaining of weakness, progressive enlargement of the abdomen and fleeting edema of the feet of six months duration. He had suffered previously from occasional attacks of fever which were at times ushered in with rigor.

The patient was a pale but well developed boy with a protuberant abdomen. The spleen was grossly enlarged occupying almost the entire abdomen, the lower pole could be felt just above the symphysis pubis. The liver was enlarged and was felt 4" below the costal margin. There was no free fluid in the abdomen or any prominent collateral venous channels. The lungs were dull at either bases with diminished air entry and occasional moist sounds. The apex of the heart was felt at the left third interspace within the mid-clavicular line. There was a localised rather harsh systolic murmur in the mitral area.

Results of Laboratory Investigations :—

Blood Picture: Total red cell count, 3,020,000 per c.mm., white cell count, 3,800 per c.mm. (persistently below 4,000), hemoglobin 6 Gm. per 100 cc., polymorphonuclears 55 per cent, lymphocytes 40 per cent, monocytes 1 per cent, eosinophils 4 per cent.

Careful and repeated examination of blood films after exercise and after parenteral administration of adrenaline, were negative for malaria parasites.

Tests for kala-azar based on the increase of the globulin fraction were repeatedly negative.

Sternal Marrow Smear: The smear revealed a predominantly reactive normoblastic marrow. Careful examination of several smears was negative for Leishman Donovan bodies, malaria parasites or intra-cellular pigments.

Stool examination revealed fair numbers of ascaris ova.

Hospital Course :—The patient was given antihelminthic treatment and his iron deficiency anemia improved considerably after treatment with adequate dosage of iron. He started having repeated and severe attacks of epistaxis and there was progressive increase of respiratory embarassment. The surgeon was consulted at this stage. He advised splenectomy after blood transfusion.

After transfusion of about 150 cc. of homologous crossmatched blood, the patient developed a rigor and the temperature shot up to 102° F. The transfusion was discontinued and the temperature came down but the patient suddenly developed acute respiratory distress, collapsed and died at 4 a.m. on 14-12-50.

Autopsy Examination :—The patient came to autopsy 5 hours after death with a clinical diagnosis of hepato-splenomegaly probably due to chronic malarial infection. The body was that of a young boy, well developed and fairly well nourished. The body length was 141 cm. Rigor mortis was present. There was no evidence of edema ; hair was normal in distribution ; ears, nasal passages and eyes were normal ; the pupils were dilated and central ; the conjunctiva pale and without any icteric tinge. The abdomen was grossly enlarged with a few prominent superficial veins. Primary incision—thoraco abdominal.

There was no free fluid in the peritoneal cavity. The whole peritoneal cavity was almost entirely filled with a grossly enlarged spleen and an enlarged liver. The pericardial and pleural cavities were free from any fluid.

Heart: Weighed 175 Gm. The epicardial fat was increased and a milk spot was present on the anterior surface of the right ventricle 3 cm. × 1.5 cm. The diameter of the mitral, tricuspid, pulmonary and aortic valves were 6, 6.5, 7 and 7 cm., respectively. The mitral valve was reduced to a funnel shaped opening. The cusps were adherent, the margins thickened and rolled in. The tricuspid valve was thickened with adherent cusps. The pulmonary and the aortic valves were normal. The coronary arteries were healthy and there was no evidence of any myocardial damage. The thickness of the left ventricular wall was 1.4 cm. and the right 0.5 cm. The aorta was healthy.

Lungs: The right lung weighed 375 Gm. and the left 325. Both were heavy and grossly edematous. There was no evidence of any infarction or collapse. The pulmonary vessels were free from any thrombi.

Spleen: Weighed 4,000 Gm. There was an area of perisplenitis, 10 cm. × 7½ cm. on the upper pole of the spleen consisting of thin flakes of fibrin. The capsule and the trabeculae were not thickened. The pulp was firm and fleshy, greyish-red in colour, the malpighian bodies could be discerned which were rather prominent under the capsule. The splenic vein was patent and normal all throughout its course and no abnormality of the vascular pattern was detected at the hilum. Prussian blue reaction on the cut surface was negative for any excess of iron.

Liver: Weighed 2,750 Gm. Soft and mottled in appearance. There were prominent rib markings on the anterior surface. The cut surface was pale, soft and mottled in appearance. The lobular pattern was indistinct but there was a peculiar congested appearance round about the portal tracts which was very striking. The prussian blue reaction for iron was negative.

No other abnormality was detected in the other parts of the gastro-intestinal tract. Two round worms were seen in the jejunum.

Kidneys: The right kidney weighed 100 Gm. and the left 75 Gm. The capsule stripped off easily leaving a rather pale surface. The cut surface showed a cortex of normal thickness with a rather indistinct cortico-medullary junction and prominent vasa recti. There was no edema of the substance and the prussian blue reaction was negative.

The rest of the urinary tract, the genitals, the suprarenals and the brain did not reveal any morphological abnormality.

Sections from all the organs and tissue were fixed in formal sublimate and paraffin sections were studied after routine hemotoxylin and eosin stain and with special stains as was found necessary.

Spleen: Showed all the classical features of fibro-congestive splenomegaly, dilated veins with collagenous thickening resulting in increased definition of the sinus wall, periarterial fibrosis, atrophy of the malpighian body, widespread and diffuse fibrosis of the stroma, thickening of the pulp chords with patchy hyperplasia of the reticulum cells, scattered periarterial hemorrhages and siderotic nodules (Figs. 1, 2, 3, 4). Section of the spleen at the hilum and at different levels of the splenic vein did not reveal any abnormality.

Liver: The lobular architecture of the organ was well preserved. The sinuses were dilated separating the radiating columns of the liver cells. The outstanding feature was the nature of the larger intra-hepatic branches of the radicles of the portal vein. The hepatic artery was accompanied by a number of lake-like thin walled channels some of which were very large. These ill formed cavernomatous channels had completely obliterated the normal radicles of the portal vein. These changes were seen in all the sections from the many blocks that were studied and corresponded with the peculiar congested areas seen on the cut surface of the liver giving it the mottled appearance at the autopsy table. There was no evidence of any cirrhosis or excess of pigments. (Fig. 5).

Heart: Sections from the mitral and tricuspid valves and the myocardium at the base of the valves revealed the tell tale appearance of old healed affection—collagenous thickening of the valves with vascularisation, healed Aschoff bodies in the myocardium at the base of the valves, patchy myocardial scars along the branches of the coronary arteries in the inter-mycial connective tissue spaces. There was no evidence of any recent active process.

Aorta and Large Blood Vessels were notmal.

Lungs: Sections from both the lungs revealed congested and dilated alveolar vessels with the alveoli filled with pink staining edema fluid. The alveolar spaces contained fair numbers of chronic heart failure cells. Some of the alveoli showed changes of acute emphysema.

Sternal Marrow: The marrow was extremely cellular. There were fair numbers of normoblasts with pyknotic nuclei but the lack of differentiation of the cells into the granulocytic series was very striking. (Fig. 8).

Kidneys: Both showed normal architecture. Under the capsule there were numbers of wide, ill-formed, thin-walled blood spaces—cavernomatous tissue. (Fig. 6).

Tongue: Under the surface epithelium there were large thin walled vascular channels surrounded by leashes of smaller thin walled vessels. (Fig. 7).

Sections from the rest of the organs and tissues did not reveal any significant abnormality except the upper jejunum which showed fair amount of cellular infiltration of the villi with lymphocytes and plasma cells, increase of fibrous tissue in cores of the villi and reactive hyperplasia of the lymph follicles. The mesenteric lymph nodes showed reactive Fleming's centre and sinus cattarrh.

DISCUSSION

The outstanding features of this case are :—

(i) Clinical : progressive hepato-splenomegaly in a young boy subjected to repeated attacks of epistaxis. He had persistent leucopenia with relative lymphocytosis and an iron deficiency anemia which responded to treatment. Investigations during life failed to establish any of the causes of gross hepato-splenomegaly, common in our country.

(ii) Autopsy revealed : (a) an enormous spleen (4,450 Gm.), showing the classical histology of fibro-congestive splenomegaly. (b) an enlarged liver having peculiar cavernomatous malformations of the intrahepatic radicles of the portal vein. (c) angiomatous condition of the subcapsular vessels of the kidney and of the tongue. (d) marked hyperplasia of the sternal marrow with a maturation defect of the cells of the granulocytic series. (e) well marked mitral stenosis with involvement of the tricuspid valve and stigmata of old rheumatic affection. The presence of heart failure cells in the pulmonary alveoli indicated certain degree of cardiac decompensation, and (f) the terminal event appears to be one of failure of the circulatory dynamics, as a result of the transfusion, which resulted in acute edema of the lungs.

Careful autopsy study failed to reveal, in this case, any of the recognised causes of fibro-congestive splenomegaly. Rousselot[10] could not demonstrate any obstructive factor in the portal venous system in as much as 40 per cent of cases. He, however, stated that a more careful search in some cases revealed some cause of portal hypertension. Apart from the recognised causes of portal hypertension mentioned in the introduction, Rousselot observed, in some of his cases, variations in the anatomical pattern of the portal vein. He was the first to suggest that congenital anomalies may account for some of the cases of fibro-congestive splenomegaly, specially occurring in the early years of life.

In the case under discussion, the normal pattern of the intrahepatic branches of the portal vein was replaced by cavernomatous channels. The effect of such large thin walled channels in the terminal parts of the portal venous system must inevitably lead to slowing down of the venous return, which in its turn will result in raised pressure in the proximal areas of the portal venous drainage. The ultimate result of such an abnormality of the anatomical pattern in its effect in the dynamics of the portal venous circulation will, therefore, be similar to the more well recognised causes of portal hypertension leading to fibro-congestive splenomegaly.

The presence of vascular hamartomas in the kidney and in the tongue lends added significance to the condition in the liver.

The widespread changes seen in the anatomical pattern of the intrahepatic branches of the portal vein occurring in a young boy suggests that such abnormalities are probably of congenital origin. Such a view in interpreting these abnormalities is strongly sustained by findings of vascular abnormalities in the spleen and in the tongue, whether vascular malformation affected the intimate splenic vasculature and added further to the altered dynamics can only be a matter of guess. This, however, is a possibility which cannot altogether be ignored.

The existence of a well established valvular lesion with evidence of certain degree of chronic cardiac decompensation may account for the rapidly progressive enlargement of the spleen and the liver and the enormous size of these organs.

The appearance of the bone marrow is significant. The cellular marrow showing lack of differentiation of the cells towards mature granulocytes conforms to the observations of Limarzy *et al.*[7] and explains the persistent leucopenia with relative granulopenia. One of the prominent symptoms was the repeated attacks of epistaxis. This may be explained on the basis of thrombocytopenia due to the associated maturation defect of the megakaryocytic tissue (Limarzi *et al.*[7]). Unfortunately, the platelet count was not done during life.

SUMMARY

The clinical summary and the detailed autopsy findings of a case of gross hepato-splenomegaly in a boy aged 15, is presented.

Cavernomatous malformations of the intrahepatic branches of the portal vein as a cause of fibro-congestive splenomegaly, is described for the first time.

The congenital nature of such anatomical variation is suggested by the presence of vascular hamartomas in the kidney and in the tongue.

Marked hyperplasia of the bone marrow but having maturation defect of the cells of the granulopoietic series, explains the persistent granulocytopenia.

The cause of repeated epistaxis in the case is suggested. Hepato-splenomegaly is very common in our country. There is, however, an unfortunate tendency to group many of such cases as chronic malaria without adequate evidence. A plea is, therefore, being made for a careful study of such cases with a view to elucidate the nature of many of the unexplained hepato-splenomegalies.

ACKNOWLEDGMENT

Our thanks are due to Principal G. L. Sharma, M. D., Dean, Medical College, Nagpur, for his permission to present the case, to Shri Shaha for the histological preparations and to Shri Joshi for the microphotographs.

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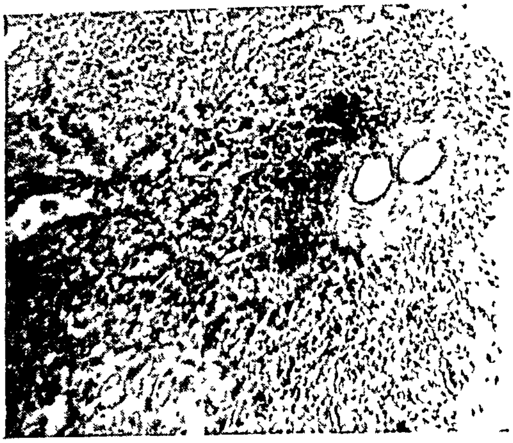

Fig. 1.—Section of spleen, under low magnification, showing thickened arterioles with periarterial hemorrhage and the thickened and dilated sinusoids.

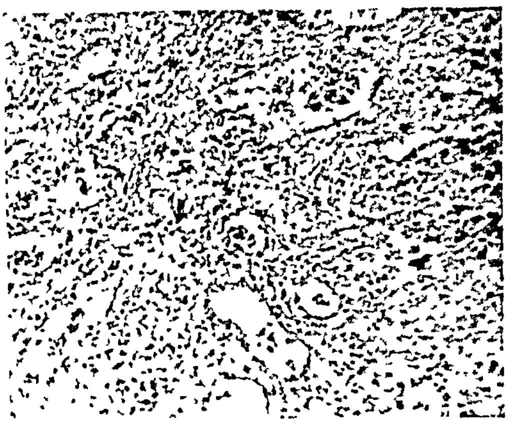

Fig. 2.—Same section, under higher magnification, showing the widely dilated sinusoids with thick walls.

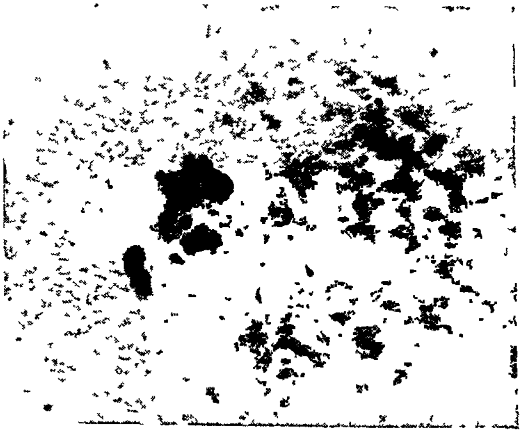

Fig. 3.—Section of spleen, stained for iron, under high magnification, showing one of the characteristic siderotic nodules.

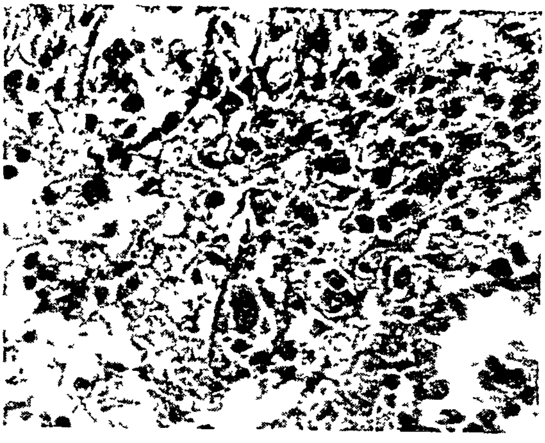

Fig. 4.—Section of spleen, under high magnification, showing an area with marked proliferation of the sinus littoral cells.

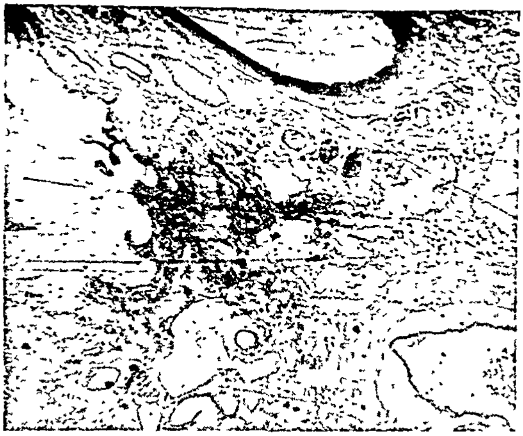

Fig. 5.—Section of liver showing the thin walled cavernomatous malformation of the intrahepatic branch of the portal vein. A thick walled hepatic artery is seen at the margin of the section.

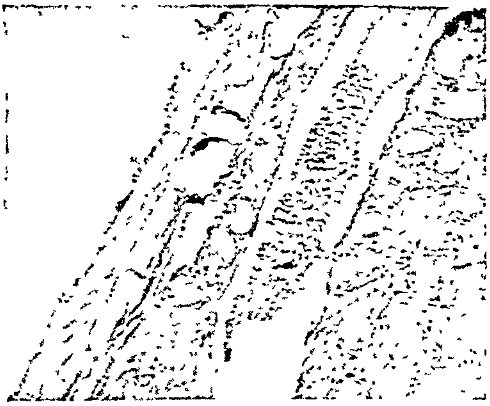

Fig. 6.—Section of kidney showing thin walled wide vascular channels in the subcapsular region.

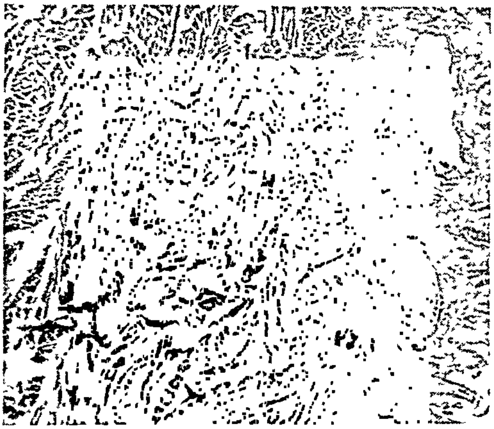

Fig. 7.—Section of tongue showing thin walled wide vascular channels under the epithelium.

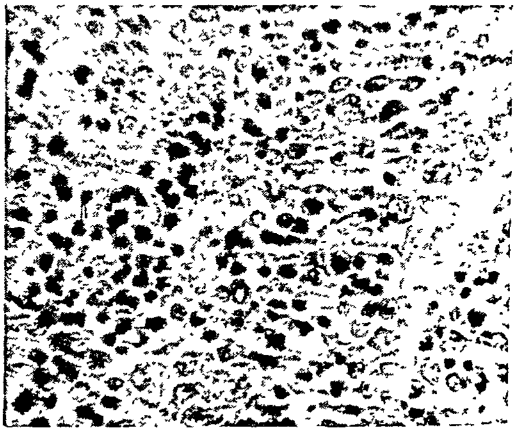

Fig. 8.—Section of the sternal marrow showing marked cellularity but absence of differentiation into the cells of the granulopoietic series.

MEDICAL TREATMENT OF EPILEPSY *

A PRELIMINARY REPORT OF 146 CASES

N. S. Valia † and N. J. Kothari †

After the establishment of the electroencephalographic department at the K. E. M. Hospital, Bombay, a large number of epilepsy cases came to the department for the brain wave tracing. We then decided to study the problem of epilepsy from different aspects. The present paper is a preliminary report based upon one year's study of 146 cases of epilepsy, from the point of view of the comparative value of the various anti-epileptic drugs.

At present, the drugs commonly used in epilepsy are the following. Bromides, first introduced by Locock[30], in 1857, was the standard treatment of epilepsy for many years. It is of use even now when other drugs fail. According to Pollock[37], bromides are the most satisfactory anticonvulsant drugs. They have certain disadvantages ; they sometimes cause mental dullness, a skin rash, confusion and occasionally produce psychotic changes when used for a long time. Phenobarbitone, first introduced by Hauptmann[21], in 1912, is a reliable anticonvulsant. Its great advantage is its low toxicity. It sometimes causes skin eruptions, lethargy and drowsiness. Prominal, similar to phenobarbitone, has an advantage over the latter drug because of its low sedative action. In large doses it also causes drowsiness. Many clinicians feel that there is no great difference in the anti-convulsive and sedative effects of the two drugs, but prominal is sometimes better tolerated than phenobarbitone. Dilantin (5.5 diphenyl hydantoin) first introduced by Merritt and Putnam[33], in 1938, is one of the significant advances in the treatment of epilepsy. It has a highly selective action on the motor area of the cortex, without depressing the other functions of the brain. Sometimes it shows toxic manifestations, like hypertrophy of the gums, skin eruptions, drowsiness, vertigo, ataxia, tremors, diplopia and gastro-intestinal irritation. Mesantoin (3 methyl, 5 phenyl, 5 ethyl, hydantoin) recently introduced by Lockalzo[30A], in 1945, is allied to dilantin. Its place in the treatment of epilepsy is still a matter of opinion ; it does not cause swelling of gums. Its toxic symptoms are fever, skin rash, enlargement of lymph glands and blood dyscrasia. Tridione, first introduced by Lennox and Goodman[27], in 1945, is of value in treatment of petit mal. It sometimes damages the kidney functions or liver functions or affects blood. Paradione, allied to tridione, is considered to be less effective

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but less toxic. Antihistaminic drugs, glutamic acid and a ketogenic diet are sometimes recommended in the treatment of epilepsy.

Because of the existence of differences of opinion regarding the value of various antiepileptic drugs, an attempt was made to study the comparative value of these drugs, to find out. if possible, the most satisfactory method of treatment of different types of epilepsy. Patients were selected from the psychiatric department of the Hospital. (The electroencephalography unit is a part of this department). Mostly, the cases with a history of a maximum interval of less than a fortnight between the two attacks were selected. One of us interviewed each patient and recorded the detailed history on a specially prepared questionnaire. Each patient was made to feel that we were especially interested in his case and advised him to report to us regularly. The cases that had been included in this study have been classified below according to age and sex.

TABLE 1.—*Classification According to Age and Sex.*

	Age					
Total No. of cases.	Below 10 Years.	11—20 Years.	21—30 Years.	31—40 Years.	41—50 Years.	51 & above.
146	25	56	49	10	4	2

	Sex			
Total No. of cases.	Male.	Female.	Male-child.	Female-child.
146	76	34	22	14

One of our difficulties was in getting the drugs for our study. Phenobarbitone was the most easily available because it was supplied by the hospital ; for the other drugs we requested some manufacturing concerns for their antiepileptic drugs. Some of them helped us in this study.

Our other difficulty was regarding the follow-up of the cases. Anyone working in the out-patient department of a general hospital in our country would appreciate how difficult it is to carry on a satisfactory follow-up. We were somewhat successful in this attempt by showing a personal interest in each patient and by explaining to them that the condition was of an erratic nature and therefore an absence of attacks for sometime after the administration of a drug, should not make them feel that they were free from the disease, but that in their own interest they should continue to report regularly. They were also told that the drugs given to them were potentially toxic and therefore a regular report to one of us was a necessary part of treatment. The drugs supplied by the firms were given by one of us personally. It was our impression that these factors were probably responsible for the follow-up for more than 12 months in many cases.

TABLE 2.—*Follow-up.*

Total No. of cases.	1 to 3 months.	3 to 6 months.	6 to 12 months.	More than 1 Year.
146	49	29	50	18

The following drugs were used in this study. Phenobarbitone, dilantin (antisacer), mesantoin, tridione, paradione and bromides.

The minimum dose of phenobarbitone for an adult in this series was 1½ grains and the maximum dose was 9 grains per day. For a child the minimum dose was 1 grain and the maximum was 6 grains per day. For dilantin the minimum dose was 2 tablets (3 grains) and the maximum dose was 6 tablets (9 grains) per day for an adult and a minimum of 1 tablet (1½ grains) and maximum of 4 tablets (6 grains) for a child. The dose of prominal in this series was 2 to 6 tablets for an adult and 1 to 3 tablets for a child. The maximum dose of tridione was 4 capsules a day. The only patient on paradione was given 2 capsules a day and the only patient on bromides was given 15 grains daily.

Thiantoin (maletoin in our country) has been kindly supplied by Lilly & Co., from the U.S.A. for this study. As the drug is only recently being studied, it is neither discussed nor reported in this paper. Phenylacetylurea (phenurone) is sent by Abbott Laboratories for this study. The drug has not reached us so far, and the results of our study of these two drugs will be presented at a later date.

The complications on administration of different drugs have been tabulated below in the following table.

TABLE 3.—*Toxic Reactions.*

Drug.	Drowsiness.	Giddiness.	Headache.	Irritability.	Vomiting.	Loss of appetite.	Ataxia.	Neutropenia.	Eosinophilia.	Jaundice.
Luminal ..	35	3	3	3	2	1	..	..	..	..
Dilantin ..	2	..	..	..	4	..	1	..	..	..
Prominal ..	3	1	..	..	..	1	..	..	..	..
Mesantoin	..	1	1	..	..	..	..	..	..	..
Paradione	..	..	..	1	..	..	..	..	..	..
Tridione ..	..	..	..	..	..	..	..	2	1	1

One case developed spongy gums with dilantin.

The table represents almost all the complications that we have come across. But certain notable features have not been included in the table. Three cases of petit mal developed grand mal after medication. Two cases of grand mal started getting petit mal after the administration of phenobarbitone. In three cases psychomotor attacks were probably precipitated by the administration of phenobarbitone.

The results of our work have been summarised below. Table 4 presents the results according to drug and Table 5 according to types of seizures. A patient was considered to have shown excellent improvement when he had no attack during the period of observation. Good improvement meant almost complete or at least markedly significant freedom from attacks, slight improvement meant only a slight decrease in the number of seizures as indicated by the significant increase in the interval between two attacks prior to medication. Incidentally, no patient in the series became worse except a case of petit mal that started getting more attacks on the administration of paradione.

TABLE 4.—*Analysis of* 146 *Cases According to Medication.*

Drug.	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	90	16	40	5	29
Dilantin	13	2	5	1	5
Mesantoin	6	2	2	..	2
Prominal	5	..	2	..	3
Tridione	4	1	..	..	3
Paradione	1	..	..	..	1
Bromides	1	..	1	..	..
Dilantin + Luminal	24	3	11	1	9
Mesantoin + Luminal	2	..	..	..	2
D.M.L.	3	1	..	..	2
A + Pr + L ..	1	..	..	..	1

TABLE 5.—*Analysis of* 146 *Cases According to Type of Seizures.*

Type of Seizures.	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Grand mal	112	20	46	6	40
Petit mal	7	2	1	..	4
Psychomotor	2	..	1	..	1
Myoclonic epilepsy ..	3	1	..	..	2
Jacksonian	5	..	3	..	2
Grand mal+ Petit mal	10	1	6	1	2
Grand mal+ Psychomotor	4	1	2	..	1
Grand mal+ Jacksonian.	1	..	..	..	1
Infantile convulsions	2	..	2	..	..

Table 6 gives the analysis of results according to each type and Table 7 according to each drug.

TABLE 6.—*Analysis According to Type.*

Grand mal (112 Cases).

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	67	15	28	4	20
Dilantin	12	1	5	1	5
Mesantoin	4	1	2	..	1
Prominal	4	..	2	..	2
Dilantin + Luminal	20	2	8	1	9
Bromides	1	..	1	..	..
D.M.L.	1	1	..	..	..
ML	2	..	..	..	2
A + Pr + L	1	..	..	..	1

Petit mal (7 Cases).

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	1	..	1	..	..
Mesantoin	1	1	..	..	..
Tridione	4	1	..	..	3
Paradione	1	..	..	..	1

Psychomotor (2 Cases).

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	1	..	..	..	1
Dilantin + Luminal	1	..	1	..	..
Luminal	3	1	..	..	2

Myoclonic epilepsy (3 Cases.)

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	3	1	..	..	2

Jacksonian epilepsy (5 Cases.)

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	3	..	2	..	1
Mesantoin	1	..	..	..	1
Dilantin + Luminal	1	..	1	..	..

Grand mal + petit mal (10 Cases.)

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Luminal	6	..	5	1	..
Prominal	1	..	..	..	1
Dilantin + Luminal	2	1	1	..	..
D. M. L.	1	..	..	..	1

Grand mal + psychomotor (4 Cases.)

Luminal	2	..	2	..	..
Dilantin	1	1	..	..	..
D. M. L.	1	..	..	..	1

Grand mal + jacksonian (1 Case).

Luminal	1	..	..	..	1

Infantile convulsions

Luminal	2	..	2	..	..

TABLE 7.—*Analysis According to Drug.*

Luminal (86 Cases.)

	Total.	Excellent.	Good improvement.	Slight improvement.	No improvement.
Grand mal	67	15	28	4	20
Petit mal	1	..	1	..	..
Psychomotor	1	..	..	..	1
Myoclonic epilepsy	3	1	..	..	2
Jacksonian	3	..	2	..	1
Grand mal + Petit mal.	6	..	5	1	..
Grand mal plus Psychomotor	2	..	2	..	..
Grand mal plus Jacksonian	1	..	..	..	1
Infantile convulsions	2	..	2	..	..

Dilantin (13 Cases.)

Grand mal	12	1	5	1	5
Psychomotor + Grand mal	1	1	..	..	..

Mesantoin (6 Cases.)

Grand mal	4	1	2	..	1
Petit mal	1	1	..	..	..
Jacksonian	1	..	..	..	1

Prominal (5 Cases.)

Grand mal	4	..	2	..	2
Grand mal + Petit mal	1	..	..	..	1

Dilantin + *Luminal* (24 Cases.)

Grand mal	20	2	8	1	9
Psychomotor ..	1	..	1	..	..
Jacksonian	1	..	1	..	..
Grand mal + Petit mal	2	1	1	..	..

Bromides (1 Case.)

Grand mal	1	..	1	..	..

Mesantoin + *Luminal* (2 Cases.)

Grand mal	2	..	..	..	2

D M L (3 Cases.)

Grand mal	1	1	..	..	..
Grand mal + Petit mal	1	..	..	..	1
Grand mal + Psychomotor	1	..	..	..	1

Tridione (4 Cases.)

Petit mal	4	1	..	..	3

Paradione

Petit mal	1	..	..	..	1

A + Pr. + L.

Grand mal	1	..	..	..	1

DISCUSSION

According to Toman[41], an ideal anticonvulsant drug should be long acting, non-sedative, highly effective and specific for one or more types of epilepsy. To this might be added one more qualification. lack of toxicity. The search for such anticonvulsant or anticonvulsants is on, but at present we are nowhere near the solution.

For grand mal, Merritt and Putnam[33] found dilantin superior to any other anticonvulsant, in 79 per cent of their cases. Merritt and Carter[34] still maintain that dilantin is the best drug so far. On the other hand Petermann[36] is more sceptical. With his experience of dilantin and mesantoin, since the time they were introduced, and of phenobarbitone for a longer time, he still maintains that phenobarbitone is the drug of choice. Recently, Ruskin[39] has come to a similar conclusion and maintains that for grand mal, phenobarbitone is the best drug. Kozol[26] is enthusiastic about mesantoin and he considers the drug less toxic than dilantin. According to De Jong[8], mesantoin is somewhat less potent and less toxic than dilantin. According to Ruskin[39], mesantoin is twice as effective but twice as toxic as dilantin. Fettermann and Victoroff[14] consider mesantoin an useful drug but more toxic than dilantin. At least seven deaths following mesantoin have been reported by various workers [2, 16, 24, 40]. David[8] and others advise mesantoin when dilantin fails. Ruskin[39] advises phenobarbitone first and dilantin or mesantoin only as a supplement. He advises the use of dilantin or mesantoin as a substitute for phenobarbitone only in rare cases when phenobarbitone fails. Incidentally, tridione has no place in the treatment of grand mal. According to Gibbs[18], and also according to De Jong[10], it is not only useless but is likely to increase the frequency of attacks.

In our series, out of 70 cases of grand mal, 44 showed satisfactory response with phenobarbitone. Out of 12 cases on dilantin, 6 responded satisfactorily. Three out of 4 cases on mesantoin also responded well. From amongst 20 cases that had not responded to any other drugs mentioned above, 10 responded well to a combination of dilantin and phenobarbitone. This shows that the anticonvulsive activity of phenobarbitone is probably at least as good as that of other drugs. Although between dilantin and mesantoin, mesantoin seems to be more satisfactory, the number of cases on each of these drugs is very small. Another noticeable feature is that the combination of dilantin and phenobarbitone is superior to phenobarbitone, dilantin or mesantoin alone. There is one case here that had not responded to any of the drugs mentioned above, but responded satisfactorily to bromides.

As mesantoin is likely to affect the blood, and as a regular blood count examination would be difficult in our country except in big cities, we believe that mesantoin should only be used in cases where phenobarbitone and dilantin have failed to show a response. As dilantin is more toxic than phenobarbitone and as its superiority over phenobarbitone is not established, we are inclined to agree with Petermann and Ruskin[39] that phenobarbitone is the drug of choice in grand mal. Its advantage apart from the low toxicity is that it is comparatively cheap and universally available. When a patient does not respond to phenobarbitone alone, we prefer to add dilantin rather than mesantoin.

Treatment of petit mal is a greater problem. According to Gibbs[18], phenobarbitone is of no value in cases of petit mal alone. Tridione is considered to be the best drug for this condition by Lennox[27], and by

Davis and Spillane[9]. But according to Lennox[27], it controls the attacks in one third of the cases only. But the drug is considered to be a toxic drug by numerous workers. Purpura[42], agranulocytosis[31] and nephrosis[43] following tridione have been reported[17]. At least four deaths have occurred after tridione administration[3],[17],[23]. According to Lennox[28], if there is grand mal with petit mal, tridione should be used with caution and only with other anticonvulsants. Paradione is less toxic but less effective than tridione, according to Davis and Lennox[29].

Dilantin is found to be useful in 25 to 30 per cent of petit mal cases. Mesantoin, according to Marburg and Helfand[32], is useful in petit mal. On the other hand, according to Fettermann and Victoroff[13], Lennox[27] and Gervin and Gibbs[17], mesantoin is of no value in petit mal. Glutamic acid[18] is sometimes of value in petit mal, but it is generally used only as an adjunct. Antihistaminic drugs are sometimes recommended for epilepsy, particularly for petit mal, but observations of Churchill and Gammon[7] would contraindicate their use. Ketogenic diet, recommend by Wilder[44] and advocated by Keith[25] and by Petermann[35], is found to be unsatisfactory by Gibbs[18] and considered to have been generally discarded by Buchanan[5] because it is expensive, distasteful, troublesome and difficult to regulate in children. Recently, Aird and Gordon[1], have tried desoxycorticosterone and found it useful in 6 out of 8 petit mal cases.

In our series of 10 petit mal with grand mal cases, 7 showed a satisfactory response. And in 7 of these that were on phenobarbitone, 5 responded satisfactorily, suggesting that in cases of petit mal with grand mal, phenobarbitone is a useful drug. Out of 7 cases of petit mal alone, 4 showed no improvement at all. Amongst the remaining three cases that responded satisfactorily, one was on phenobarbitone, one was on mesantoin and one was on tridione. These results do not give any idea as to which drug is satisfactory in petit mal. In a series of 5 cases treated by one of us with mesantoin in private practice and followed up for more than 18 months regularly but not included in this series, three were free from attacks, one showed satisfactory response (four attacks in 18 months instead of 2 attacks per week before mesantoin) and one became worse. On including these cases, it would seem that mesantoin is probably more satisfactory than other drugs in treatment of petit mal.

Psychomotor attacks, according to Gibbs[36], do not respond to phenobarbitone. Dilantin is useful in psychomotor attacks according to Merritt and Cartar[34]. Harris and Otto[22] found mesantoin useful in 13 out of 20 cases. De Jong[11],[12]. considers tridione useful in psychomotor attacks, but Peterman[36] has found it of no value in this condition. Gibbs[19] advocated phenurone for these attacks. Davidson and Lennox[8A] consider that this drug should not be given in liver damage. According to Carter and others[6], phenurone is not superior to other drugs and is likely to give rise to blood dyscrasias, hepatitis and psychiatric disturbances, particularly depression. Forster[15] found that 1/3 to 2/3 of his cases of psychomotor attacks responded to dilantin and phenobarbitone, 2/3 of the remaining cases responded to phenurone, but as the drug was toxic, only half of the patients could continue phenurone medication.

In our series, phenurone has not been tried so far. Out of 4 cases of psychomotor attacks with grand mal, 2 on phenobarbitone and one on dilantin responded well, and one on dilantin, mesantoin and phenobarbitone did not respond. Out of 2 cases of psychomotor attacks, one on phenobarbitone failed to respond and one on phenobarbitone with dilantin responded satisfactorily. These results do not seem to be of significance except that dilantin and phenobarbitone are likely to be of value in many of these cases.

CONCLUSIONS

In view of these observations, we provisionally recommend the following therapeutic approach towards a case of epilepsy. In every case of epilepsy, except petit mal alone, it is advisable to give phenobarbitone first. The initial dose in a child might be 1 grain and in an adult one and a half grain. The dose might be increased upto 6 grains in a child and upto 9 grains in an adult, unless the patient shows drowsiness or irritability or some behaviour disturbances. If the patient is not free from the attacks till the maximum dose is reached, dilantin might be added to phenobarbitone. Rare cases that show toxicity to phenobarbitone might be given dilantin first. The initial dose of dilantin should be 2 tablets a day and might be increased upto 4 tablets in a child and six tablets in an adult. If the attacks are not controlled by now or if the patient shows toxic manifestations, mesantoin might be given instead of dilantin. The initial dose of mesantoin should be half tablet per day and might be increased upto 6 to 12 tablets per day, unless the patient shows toxicity to the drug. The blood count of every patient on mesantoin should be done at least once a month during the administration of the drug.

So far as petit mal is concerned our experience is very small. At present we are of the opinion that in cases of petit mal alone mesantoin might be tried first. If there is no response or if the patient shows toxic manifestations, tridione might be given with regular physical examination and blood counts at least once a fortnight to avoid any complications.

SUMMARY

Considering the lack of uniformity of opinion regarding the value of the various anti-epileptic drugs, an attempt was made at the Psychiatric Department, K. E. M. Hospital, Bombay, to evaluate the comparative value of common anti-epileptic drugs.

The present paper is a preliminary report based upon the impressions of a study of 146 cases for about six months to one year. The results of the investigations have been discussed in relation to the publication of similar workers in the field.

A line of treatment for an average case of epilepsy has been suggested.

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Dilantin sodium (P. D. & Co.) and antisacer (Wanders) having a similar formula have been reported as dilantin only.)

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